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Histone Modification and Breast Cancer

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1. Introduction

In eukaryotic cells, DNA is maintained in a highly ordered and condensed form via its association with small, basic histone proteins. The fundamental subunit of chromatin, the nucleosome, is composed of an octamer of four core histones, an H3/H4 tetramer and two H2A/H2B dimers, around which 146 bp of DNA are wrapped. Dynamic modulation of chromatin structure, that is, chromatin remodeling, is a key component in the regulation of gene expression, apoptosis, DNA replication and repair and chromosome condensation and segregation. Enzymes that eovalently modify histones control many cellular processes by affecting gene expression. These modifications of core histones mainly include of methylation, acetylation, phosphorylation, ubiquitination/sumoylation, ADP-ribosylation, deamination, and proline isomerisation (Ito, 2007; Bartova et al., 2008). The abnormal regulation of these processes is intimately associated with human diseases, including cancer.

Breast cancer, the leading cause of death from cancer in women, is a heterogeneous disease ranging from premalignant hyperproliferation to invasive and metastatic carcinomas (Jemal et al., 2011). The disease progression is poorly understood but is likely due to the accumulation of genetic mutations leading to widespread changes in gene expression. Accumulating evidence has suggested that abnormal alteration of histone modification plays roles in the process of breast cancer. This chapter will summarize the relationship between histone modification and the molecular mechanism of breast cancer, and the therapy strategies focused on histone modification for breast cancer will also be discussed.

2. Histone modification and breast cancer

2.1 Chromatin structure and histone modifications

Chromatin is the physiological template of eukaryotic genome. Its fundamental unit, the nucleosome core particle, contains ~200 bp of DNA, organized by an octamer of small, basic proteins. The protein components are histones (two copies of each highly conserved core histone protein – H2A, H2B, H3 and H4). They form an interior core; the DNA lies on the surface of the particle. Nucleosomes are an invariant component of euchromatin and heterochromatin in the interphase nucleus, and of mitotic chromosomes. The nucleosome core particle represents the first level of organization, with a packing ratio of ~6. The second level of organization is the coiling of the series of nucleosomes into a helical array

to form the fiber with ~30 nm diameter, which is found in both interphase chromatin and mitotic chromosomes. This brings the packing ratio of DNA to ~40 in chromatin. The fiber-like structure requires additional proteins, which has not been well defined. The final packing ratio is determined by the third level of organization, the packaging of the 30 nm fiber itself. This gives a total packing ratio of ~ 1000 in euchromatin, cyclically interchangeable with packing into mitotic chromosomes to reach an overall ratio of ~10,000. Heterochromatin generally has a packing ratio -10,000 in both interphase and mitosis (Fig 1) (Lewin, 2004).

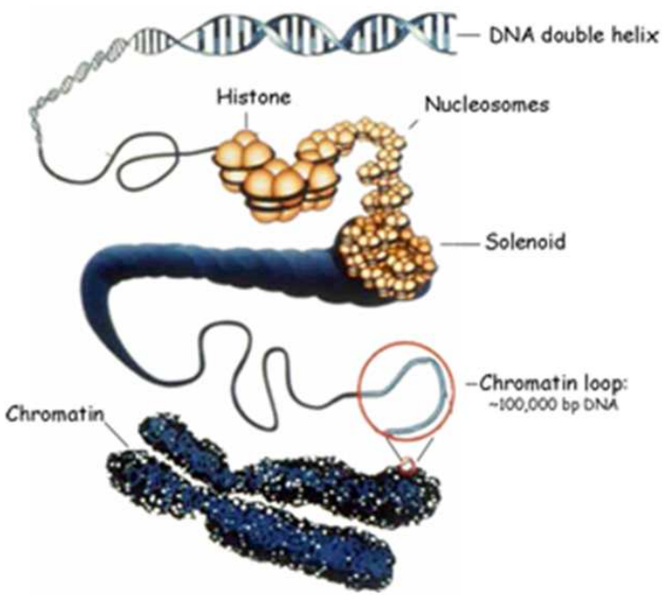

Fig. 1. Chromatin structure in eukaryotic cells

Local chromatin architecture is now generally recognized as an important factor in the regulation of gene expression. This architecture of chromatin is strongly regulated by post-translational modifications of the N-terminal tails of the histones. Core histones are subjected to a wide range of covalent modifications including methylation, acetylation, phosphorylation, ubiquitination, sumoylation, ADP ribosylation, deamination, prolineisomerization (Fig 2) (Jovanovic et al., 2010). These modifications lead to a combinatorial histone code that demarcates chromatin regions for transcription activation or repression. Although the histone code is not fully investigated, specific marks such as lysine acetylation (H3K9ac, H3K18ac, and H4K12ac), lysine trimethylation (H3K4me3), and arginine dimethylation (H4R3me2) are generally associated with transcriptionally active gene promoters, whereas some other modifications such as lysine methylation (H3K9me2, H3K9me3 and H4K20me3) are associated with transcriptional repression. Global loss of acetylation (K16) and trimethylation (K20) of histone H4 have been shown to be characteristic of human cancer (Elsheikh et al., 2009).

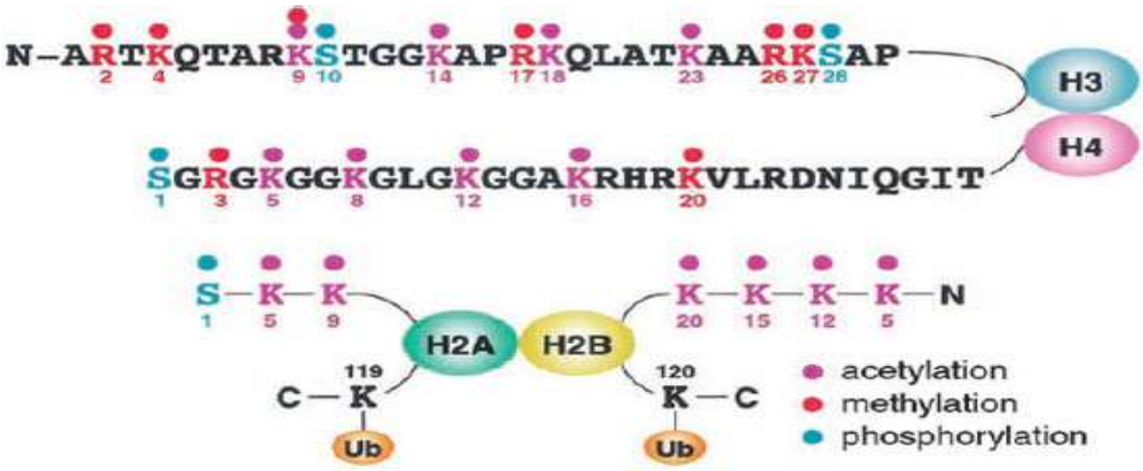

Fig. 2. Major sites of histone modifications

2.2 Histone modifications in breast cancer

2.2.1 Histone acetylation in breast cancer

Histone acetylation is a dynamic process directed by histone acetyltransferases (HATs) and histone deacetylases (HDACs). Normally, Transcription factors recruit coactivators with HAT activity to regulatory DNA sites, whereas transcriptional repressors recruit corepressors with HDAC activity (Sun et al., 2001). A summary of known HAT proteins is presented in Table 1 (Sterner et al., 2000; Yang, 2004; Kimura et al., 2005).

Many HATs have also be showed to be involved in breast cancer. Among of them, p300/CBP and NCOAs are the most important and well-characterised HAT proteins associated with breast cancer.

2.2.1.1 p300/CBP

p300 and its close homolog CBP (CREB-binding protein) are often referred to as a single entity. p300 and CBP share several conserved domains: (1) the bromodomain (Br), which is frequently found in mammalian HATs; (2) three cysteine-histidine (CH)-rich domains (CH1, CH2 and CH3); (3) a KIX domain; and (4) an ADA2-homology domain, which shows extensive similarity to Ada2p, a yeast transcriptional co-activator. The N- and C-terminal domains of p300/CBP can act as transactivation domains, and the CH1, CH3 and the KIX domains are likely to be important in mediating protein-protein interactions, and a number of cellular and viral proteins bind to these regions. The acetyl-transferase domain is located in the central region of the protein, and the Br domain could function in recognising different acetylated motifs (Fig 3A, B) (Chan et al., 2001). p300/CBP contribute to acetylation of H3-K56 and promotes the subsequent assembly of newly-synthesized DNA into chromatin (Das et al., 2009). It is a non-DNA-binding transcriptional coactivator which stimulates transcription of target genes by interacting, either directly or through cofactors, with numerous promoter-binding transcription factors such as CREB, nuclear hormone receptors, and oncoprotein-related activators such as c-Fos, c-Jun, c-Myb and AML1 (Fig 3C) (Kitabayashi et al., 1998; Sterner et al., 2000).

Family	Members	Histone specificity	Basic functions
P300/CBP		H2A/H2B/H 3/H4	Global transcriptional coactivator
Nuclear receptor coactivators (p160, SRC)	NCOA1 (SRC-1)	H3/H4	Nuclear receptor coactivators (transcriptional response to hormone signals)
	NCOA2 (SRC-2)		
	NCOA3 (SRC-3)		
GNAT			
	Hat1	H4	Histone deposition, chromatin assembly and gene silencing
	Gcn5	H3/H4	Transcriptional coactivator
	PCAF	H3/H4	Transcriptional coactivator
MYST			
	Tip60	H2A/H3/ H4	Transcriptional co-regulator, DNA repair and apoptosis
	MOZ	H3	Transcriptional coactivator
	MORF	H2A/H3/ H4	Transcriptional coactivator (strong homology to MOZ)
	HBO1	H3/H4	DNA replication, transcriptional corepressor
$TAF_{II}250$		H3/H4	TBP-associated factor, transcription initiation, kinase and ubiquitin ligase
TFIIIC		H3/H4	RNA polymerase III transcription initiation
	TFIIIC220		
	TFIIIC110		
	TFIIIC90		
ATF-2		H4/H2B	Transcriptional activator
CIITA		H4	Transcriptional coactivator
CDY		H4	Histone-to-protamine transition during spermatogenesis

Table 1. Summary of major human HATs

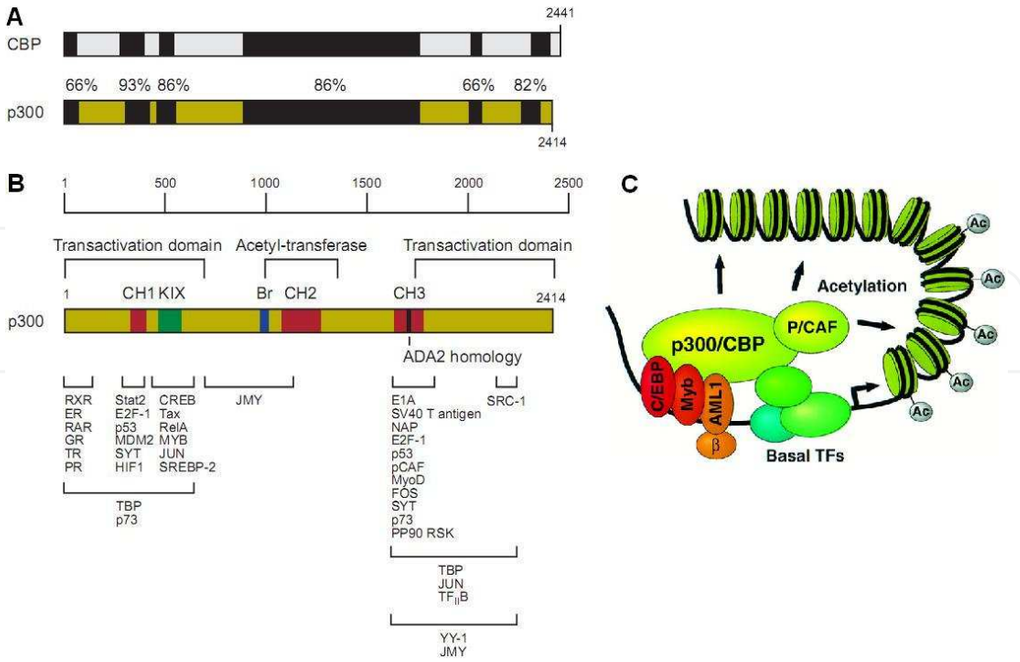

Fig. 3. Organisation of p300/CBP proteins. (A) Comparison of p300 and CBP. The dark regions indicate the areas of highest homology; (B) The functional domains in p300; (C) One of the potential model for the action of p300/CBP in the transcriptional regulation (Kitabayashi et al., 1998; Sterner et al., 2000).

p300/CBP is a ubiquitously expressed, global transcriptional coactivator that is involved in most important cellular programs, such as cell cycle control, differentiation, and apoptosis. Mice nullizygous for p300 or double heterozygous for p300 and CBP showed defects in neurulation and heart development, and then exhibited embryonic lethality, and mutations in p300 and CBP are associated with certain human disease processes (Giles et al., 1998; Yao et al., 1998; Giordano et al., 1999). A role for p300 in tumor suppression has been proposed by the fact that disturbance of p300 function by viral oncoproteins is essential for the transformation of rodent primary cells and, consistent with this hypothesis, mutations of p300 have been identified in certain types of human cancers, including breast carcinomas (Gayther et al., 2000).

It showed that both the localization of p300 and the recruitment to aggresomes differ between breast cancers and normal mammary glands. The expression level of p300 in breast cancer epithelia is higher than that in normal mammary gland. Cytoplasmic localization of p300 was also observed in tumor epithelia whereas nuclear localization was found in normal mammary glands in both animal models and in non-malignant adjacent areas of human breast cancer specimens. Proteasomal inhibition induced p300 redistribution to aggresomes in tumor but not in normal mammary gland-derived cells (Fermento et al., 2010).

The regulation of gene expression by nuclear receptors (NRs) controls the phenotypic properties and diverse biologies of target cells. In breast cancer cells, estrogen receptor alpha (ERα) is a master regulator of transcriptional stimulation and repression (Frasor et al., 2003). Upon E2 treatment, gene transcription is widely impacted, creating highly complex regulatory networks whose ultimate goal is the stimulation or suppression of specific biological processes. p300/CBP can function as a transcriptional cofactor of ERs and other

nuclear hormone receptors (Hanstein et al., 1996). Compared to CBP, NRIP1 and NCOAs, which play more gene-specific roles in the ER-dependent transcription, p300 seemed to be the only cofactor that appeared to be recruited at all the target genes of ER and plays a central role in both transcriptional activation and repression. After E2 treatment, ERα recruits coactivator complexes including of p300 and initiates transient stimulation of transcription via binds to ERα binding sites of target genes. If it could offer a more stable nucleation site for coactivator proteins (i.e. SRC-3), leading to histone acetylation and engagement of RNA polymerase II (Pol II), the transcriptional activation status would be maintained. Alternatively, ERα can cause transcriptional repression by recruiting, via p300, CtBP1-containing repressor complexes which lead to RNA polymerase II dismissal and histone deacetylation (Fig 4) (Stossi et al., 2009). In addition, the breast cancer susceptibility gene BRCA1 can strongly inhibits the transcriptional activity of ERα in human breast and prostate cancer cell lines, and this event is correlates with its down-regulation of p300 (but not CBP) (Fan et al., 2002). p300 also plays roles in the regulation of CYP19 I.3/II (aromatase), the key enzyme in estrogen biosynthesis and an important target in breast cancer (Subbaramaiah et al., 2008).

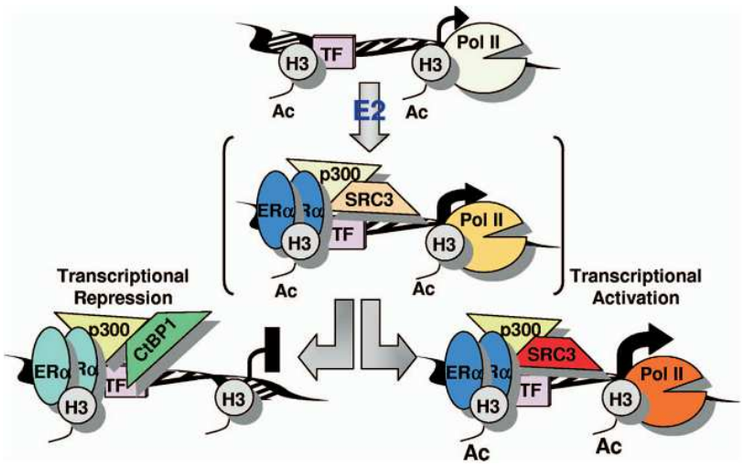

Fig. 4. Proposed model for ERα-mediated activation or repression of target genes via p300 (Stossi et al., 2009).

Another important role of p300 in breast cancer is the regulation of p53, a famous tumor suppressor. p53 can be acetylated by p300 in response to DNA damage to regulate its DNA-binding and transcriptional functions (Yuan et al., 1999). What's more, the N terminus of p300/CBP exhibits the ubiquitin ligase E3/E4 activity and is required for physiologic p53 polyubiquitination and degradation. Depletion of CBP or p300 could enhance the stabilization of p53 (Grossman et al., 2003; Shi et al., 2009).

Furthermore, p300/CBP has also been identified as a coactivator of HIF1α (hypoxia-inducible factor 1 alpha), and thus plays a role in the stimulation of hypoxia-induced genes (such as VEGF, GLUT1, etc) and development of glycolysis, which is the most important metabolic marker of cancer (Ruas et al., 2005).

2.2.1.2 Nuclear receptor coactivators

The Nuclear receptor coactivator family (NCOA), also named as p160 or steroid receptor coactivator, contains three homologous members: NCOA1 (SRC-1), NCOA2 (SRC-2, GRIP1

or TIF2) and NOCA3 (SRC-3, p/CIP, RAC3, ACTR, AIB1 or TRAM-1). These three members have an overall sequence similarity of 50–55% and sequence identity of 43–48%. They contain three structural domains. The N-terminal basic helix-loop-helix-Per/ARNT/ Sim (bHLH-PAS) domain is the most conserved region and is required for interact with several transcription factors (such as myogenin, MEF-2C and TEF, but not be obligator for NRs) and then enhance the transcription (Onate et al., 1995; Belandia et al., 2000). The central region contains three LXXLL (L, leucine; X, any amino acid) motifs, which form an amphipathic α-helix and are responsible for interacting with NRs (Heery et al., 1997; Darimont et al., 1998). The C-terminus contains two intrinsic transcriptional activation domains (AD1 and AD2). The AD1 region binds p300/CBP (but not interact with NRs), and this recruitment of p300/CBP to the chromatin is essential for NCOA-mediated transcriptional activation (Yao et al., 1996). The AD2 domain interacts with histone methyltransferases, coactivator-associated arginine methyltransferase 1 (CARM1) and protein arginine methyltransferases (PRMT1) (Koh et al., 2001). Based on such molecular features, NCOAs interact with ligand-bound nuclear receptors and recruit histone acetyltransferases and methyltransferases to specific enhancer/promotor regions, which in turn results in chromatin remodeling, assembly of general transcription factors and recruitment of RNA Polymerase II for transcriptional activation (Fig 5) (Zhang et al., 2004; Xu et al., 2009). Furthermore, The C-termini of NCOAs itself also contain HAT activity domains (Chen et al., 1997; Spencer et al., 1997), and the poly Q encoding sequence in the C-terminal of NCOA3 gene is genetically unstable and is an easy target for somatic mutations in cancer cells (Wong et al., 2006).

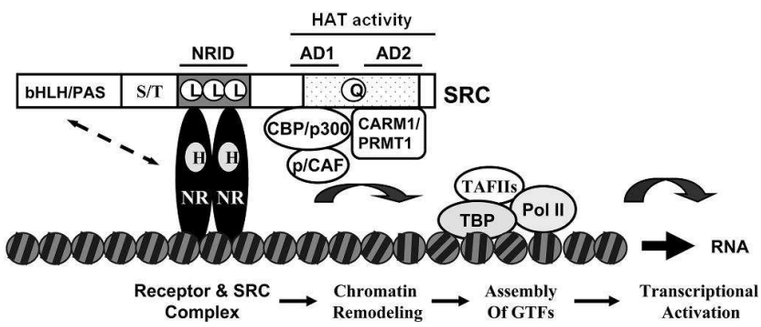

Fig. 5. Molecular structure of NCOAs and their functional mechanisms in steroid hormone-induced gene expression. Abbreviations: H, hormone; NRID, NR interaction domain; TBP, the TATA binding protein; TAFIIs, TBP-associated general transcription factors (GTFs).

Except of NRs, NCOAs also serve as coactivators for many other transcription factors associated with breast cancer, such as HIF1, NF-κB, E2F1, p53, RB and MRTFs (Zhang et al., 2004; Xu et al., 2009). By regulating a broad range of gene expression controlled by NRs and non-NR transcription factors, NCOAs regulate diverse events in the development of breast cancer. Either NCOA1 or NCOA2 deficiency can reduce ductal side branching and alveologenesis in the mammary gland (Xu et al., 1998; Mukherjee et al., 2006), and NCOA3$^{-/-}$ mice show growth retardation, delayed puberty, reduced female reproductive function and blunted mammary gland development (Xu et al., 2000).

In normal human breast, the levels of the three NCOA proteins in epithelial cells are usually low or undetectable (Hudelist et al., 2003). NCOA1 is overexpressed in 19% to 29% of breast cancers and plays important roles in cell proliferation, lymph node metastasis, disease recurrence and poor disease-free survival (DFS) (Fleming et al., 2004). Therefore, elevated

NCOA1 has been regarded as an independent predictor of breast cancer recurrence following therapy (Redmond et al., 2009). Although the evidence were not very sufficient, NCOA2 overexpression might also promote proliferation and invasion of breast cancer cells (Kishimoto et al., 2005). The amplification (in less than 10%) and elevated expression (in over 30%) of NCOA3 were be detected in breast cancer, and its overexpression in breast cancer usually correlates with the expression of ERBB2 , matrix metalloproteinase 2 (MMP2), MMP9 and PEA3 and with larger tumor size, higher tumor grade, and/or poor DFS (Anzick et al., 1997; Hudelist et al., 2003; Harigopal et al., 2009; Xu et al., 2009). What's more, elevated NCOA3 is able to promote estrogen-independent cell proliferation depends on the function of E2F1 and the association between NCOA3 and E2F1, but not ER (Louie et al., 2004).
In addition, NCOAs play important roles in the chemotherapy resistance of breast cancer. Increased expression levels of the ER-NCOA3 complex were found in tamoxifen-resistant cells, and such overexpression of NCOA3 could enhance the agonist activity of tamoxifen and therefore, reduces its antitumor activity in patients with breast cancer (Smith et al., 1997; Zhao et al., 2009).

2.2.1.3 HDACs

The 18 HDACs identified so far can be categorized into four classes: class I (HDAC1–3, HDAC8), class II (HDAC4–7, 9–10), class III (Sirtuin1–7) and class IV (HDAC11). Class I, II, and IV HDACs share homology in both sequence and structure and all require a zinc ion for catalytic activity. In contrast, class III HDACs shares no similarities in their sequence or structure with class I, II, or IV HDACs and requires nicotinamide adenine dinucleotide (NAD+) for catalytic activity (Ellis et al., 2009; Mottet et al., 2010). HDACs remove the acetyl groups from histone lysine tails and are thought to facilitate transcriptional repression by decreasing the level of histone acetylation. Like HATs, HDACs also have non-histone targets (Bolden et al., 2006; Wang et al., 2007).
Several HDACs have been found to be involved in breast cancer. In ER-positive breast cancer MCF-7 cells, expression of HDAC6 was increased after being treated by estradiol, and the elevated HDAC6 could deacetylate alpha-tubulin and increase cell motility. While the ER antagonist tamoxifen (TAM) or ICI 182,780 could prevent estradiol-induced HDAC6 upregulation, and then reduce cell motility. The *in vivo* assays showed that the patients with high levels of HDAC6 mRNA tended to be more responsive to endocrine treatment than those with low levels, indicating that the levels of HDAC6 expression might be used as both as a marker of endocrine responsiveness and also as a prognostic indicator in breast cancer (Zhang et al., 2004; Saji et al., 2005). Besides, HDAC1, Sirtuin3 (SIRT3), SIRT7 are all overexpressed in breast cancer (Zhang et al., 2005; Michan et al., 2007; Saunders et al., 2007). HDAC4 overexpression and mutations have also been found in breast cancer samples (Sjoblom et al., 2006).

2.2.2 Histone methylation in breast cancer

Histones can be mono-, di-, or tri-methylated at lysine or arginine residues by histone methyltransferases (HMTs). Many HMTs, including both lysine-specific HMTs (eg. SMYD3) and arginine-specific HMTs (eg. PRMT1 and CARM1), have been shown to act as ER coactivators and be involved in breast cancer.

2.2.2.1 Histone lysine methyltransferase (HKMTs)

Histone lysine methylation occurs on histone H3 at ε-amino group of lysines 4, 9, 14, 27, 36, and 79 and on histone H4 at lysines 20 and 59 (Strahl et al., 2000; Lee et al., 2005). In general,

methylation at H3K4 or H3K36, mono- methylations of H3K27, H3K9, H4K20, H3K79, and H2BK5 is associated with transcriptional activation, whereas trimethylations of H3K27, H3K9 H3K79, and H4K20 are linked to transcriptional repression (Rea et al., 2000; Kouzarides, 2007; Wang et al., 2007). Many HKMTs have been isolated and characterized (Tab 2). Up to now, except of Dot1, all the HKMTs contains a conserved SET [Su(var), Enhancer of zeste, trithorax] domain that is responsible for catalysis and binding of cofactor S-adenosyl-l- methionine (AdoMet), and many of them has been shown to play roles in the breast cancer.

NSD3 is amplified in human breast cancer cell lines and primary tumors and identified at the breakpoint of t(8;11)(p11.2;p15), resulting in a fusion of the NUP98 and NSD genes (Angrand et al., 2001; Rosati et al., 2002).

SMYD3 is a novel SET-domain-containing lysine histone methyltransferase which has been regarded as an important factor in carcinogenesis. Formed a complex with RNA polymerase II through an interaction with the RNA helicase HELZ, SMYD3 specifically methylates H3K4 and activates the transcription of a set of downstream genes (including of Nkx2.8, hTERT, WNT10B, VEGFR1, c-Met, etc) containing a ‘‘5′ - CCCTCC - 3′’’ or “5′ - GGAGGG - 3” sequence in the promoter region (Fig 6) (Hamamoto et al., 2004; Hamamoto et al., 2006; Kunizaki et al., 2007; Zou et al., 2009). It seems that the N-terminal region of SMYD3 plays an important role for the regulation of its methyltransferase activity, and the cleavage of 34 amino acids in the N-terminal region or interaction with heat shock protein 90 alpha (HSP90α) may enhance the histone methyltransferase (HMTase) activity compared to the full-length protein (Silva et al., 2008). Enhanced expression of SMYD3 is essential for the growth of many cancer cells (such as breast cancer, colorectal carcinoma, hepatocellular carcinoma, etc), and it also could stimulate cell adhesion and migration, whereas suppression of SMYD3 by RNAi or other reagents induces apoptosis and inhibits cell proliferation and migration (Hamamoto et al., 2004; Hamamoto et al., 2006; Luo et al., 2007; Wang et al., 2008; Luo et al., 2009; Zou et al., 2009; Luo et al., 2010). SMYD3 may be an important coactivator of estrogen receptor (ER) in the estrogen signal pathway. It can directly interact with the ligand binding domain of ER, in turn augments ER target gene expression via histone H3-K4 methylation (Kim 2009).

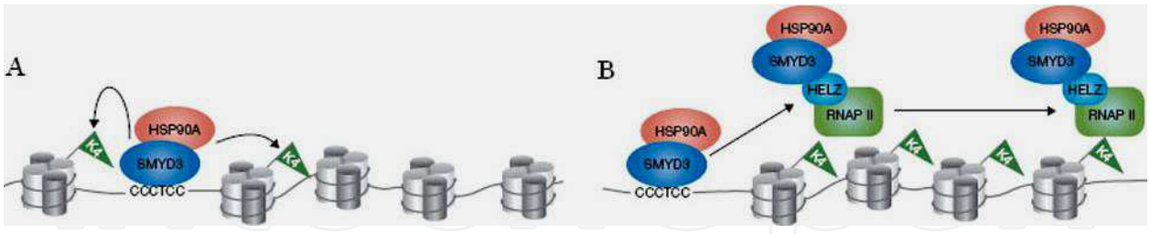

Fig. 6. SMYD3-mediated histone H3-K4 methylation and transcriptional regulation. (Sims et al., 2004)

EZH2 overexpression has been found in breast cancer, its elevation is associated with poor prognosis. It seems that EZH2 might be associated with the regulation of pRB–E2F pathway and genes involved in homologous recombination pathway of DNA repair (Zeidler et al., 2005). However, the detailed mechanism of EZH2 in cancer is not yet clear. Another study has shown that EZH2 is also overexpressed in preneoplastic breast lesions and morphologically normal breast epithelium adjacent to the pre-invasive and invasive lesions, indicating that it might be a marker of epithelium at higher risk for neoplastic transformation (Ding et al., 2006).

Family	Members	Histone specificity	Basic functions
SET domain-containing proteins			
SUV39	SUV39H1, SUV39H2, SULT1E1, G9A, CLLL8	H3K9	Transcriptional repression
SET1	MLL1, MLL2, MLL3	H3K4	Transcriptional activation
SET2	NSD1	H3K36, H4K20	Transcriptional activation
	NDS2	H4K20	Transcriptional activation
	NSD3	H3K4, H3K27	Mainly be transcriptional repression
	SETD2	H3K36	Transcriptional activation
SMYD	SMYD1	H3K4	Transcriptional repression
	SMYD2	H3K36	Transcriptional activation
	SMYD3	H3K4	Mainly be transcriptional activation
	SMYD4	Unclear	Transcriptional repression
	SMYD5	Unclear	Unclear
EZ	EZH2	H3K27	Transcriptional repression
SUV4~20	SUV4~20H1, SUV4~20H2	H4K20	Heterochromatin
PRDM2		H3K9	Transcriptional activation
Others	SET7/9	H3K4	Transcriptional activation
	SETD8	H4K20	Transcriptional repression
	SETDB1	H3K9	Transcriptional repression
	EHMT1	H3K9, H3K27	Transcriptional repression
Non-SET domain-containing proteins			
Dot1	Dot1L	H3K79	Transcriptional repression

Table 2. Summary of major human HKMTs (Pan et al., 2010)

PRDM2 (RIZ1) was originally identified as a pRb-binding protein, and its inactivation and underexpression via mutations or promoter hypermethylation had been found in a number of tumors including breast, colon, liver and lung cancers, as well as neuroblastoma, melanoma and osteosarcomas (Kim et al., 2003; Wang et al., 2007). Overexpression of PRDM2 induces G2/M cell-cycle arrest and apoptosis in tumor cell lines, while PRDM2$^{-/-}$ mice are prone to developing B cell lymphoma and stomach cancer (Steele-Perkins et al., 2001; Gibbons, 2005).

2.2.2.2 Histone arginine methyltransferase (HRMTs)

The protein arginine methyltransferase (PRMT) family is the major HRMTs up to now. The PRMTs are classified into four groups depending on the type of methylarginine they generate: Type I PRMTs (PRMT1, PRMT2, PRMT3, PRMT4, PRMT6 and PRMT8) catalyze the formation of ω-NG, monomethylarginines (MMA) and ω-NG, NG-asymmetric dimethylarginines (aDMA); Type II PRMTs (PRMT5, PRMT7 and PRMT9) catalyze the formation of MMA and ω-NG, N'G-symmetric dimethylarginines (sDMA); Type III PRMTs (remained unclear) catalyze only the monomethylation of arginine residues in proteins; Type IV PRMTs (only be found in *Saccharomyces cerevisiae* up to date) catalyze the methylation at delta (Δ) nitrogen atom of arginine residues (Niewmierzycka et al., 1999; Boisvert et al., 2005; Bachand, 2007).

Compared to HKMTs, The evidence for the involvement of HRMTs in human cancers is not as solid. However, underexpression of PRMT1 has been observed in breast cancer (Scorilas et al., 2000). PRMT4, also known as coactivator-associated arginine methyltransferase-1 (CARM1), is a coactivator for nuclear receptors and is oversexpressed in prostate and breast cancers (El et al., 2006). PRMT4 plays an important role in estrogen-induced cell cycle progression in the MCF-7 breast cancer cell line. Upon estrogen stimulation, the E2F1 promoter is subject to PRMT4-dependent dimethylation on H3R17, and this recruitment of PRMT4 by ERα are dependent on the presence of the NCOA3 (Frietze et al., 2008).

2.2.2.3 Histone demethylase

It used to be considered that histone methylation was a permanent and irreversible histone modification. However, in recent decade, many enzymes have been identified with the ability to demethylate methylated histone lysine/arginine residues via amine oxidation, hydroxylation or deimination (Cloos et al., 2008). The histone demethylases could be divided into three distinct classes. The first class (petidylarginine deiminase 4, PADI4) converts a methyl-lysine to citrulline. The second class (lysine-specific demethylase 1, LSD1) reverses histone H3K4 and H3K9 modifications by an oxidative demethylation reaction. The third class of demethylases is the family of Jumonji C (JmjC)-domain containing histone demethylases (JHDMs). Contrast to LSD1, JHDMs can demethylate all three methylated states (mono- di- and tri-methylated lysine). Up to now, JHDMs have been found to demethylate H3K36 (JHDM1), H3K9 (JHDM2A) and H3K9/K27 (JHDM3 and JMJD2A-D) (Klose et al., 2006; Miremadi et al., 2007).

Histone demethylase JARID1B (PLU-1) is shown to be overexpressed in breast cancers but low expressed in normal adult tissues, and it is essential for the proliferation of the MCF-7 breast cancer cell line and for the tumor growth of mammary carcinoma cells in nude mice. Several target genes of JARID1B have also been identified to be associated with breast cancer proliferation, such as 14–3–3σ, BRCA1, CAV1, and HOXA5 (Lu et al., 1999; Yamane

et al., 2007). LSD1 might be a coactivator in the ER signalling (Garcia-Bassets et al., 2007). JMJD1C expression is decreased in breast cancer tissues compared with normal breast tissues, indicating that it might be a tumor suppressor (Wolf et al., 2007).

2.2.3 Histone phosphorylation in breast cancer

Phosphorylation is also thought to have a role in chromatin remodeling and in the initiation of gene transcription, and therefore be associated with the development of human cancer (Espino et al., 2006; Wang et al., 2007). Phosphorylation of H3 on S10 and S28 is important not only during mitotic chromosome condensation but also in transcriptional activation of immediate early genes. The number of H3 pS10 foci was increased, and these TPA-induced foci were positioned next to actively transcribed regions in the nucleus after TPA stimulating of MCF-7 breast cancer cells. Presumably, these nuclear sites represent the nuclear location of genes that are induced or in a competent state. Thus, growth factors stimulating the Ras/MAPK and increasing H3 pS10 at transcriptionally active loci may contribute to aberrant gene expression and breast cancer progression (Espino et al., 2006).

2.2.4 The other histone modifications in breast cancer

Besides the acetylation, methylation and phosphorylation, there are some other modification occurred in the histone. These epigenetic changes include ubiquitination/sumoylation, ADP-ribosylation, deamination, and proline isomerisation. Although the knowledge of their functions and mechanisms is still little, some studies have showed that they are also associated with breast cancer and other human cancers.

The regulation of gene expression by phosphorylated and undersumoylated PRs is a novel form of hormone independent PR action that is predicted to contribute to breast cancer cell growth and survival (Daniel et al., 2009). Recent studies revealed that E3 ubiquitin ligases play important roles in breast carcinogenesis. ubiquitin-mediated protein degradation plays an important role in many cancer-related cellular processes. E3s play critical roles because they control the substrate specificity. Accumulating evidence suggests that genetic and expression alteration of E3s contributes to breast carcinogenesis (Chen et al., 2006).

histone sumoylation as a component of the group of modifications that appear to govern chromatin structure and function to mediate transcriptional repression and gene silencing (Shiio et al., 2003). A better understanding of the epigenetic mechanisms that cause transcriptional repression has allowed researchers to find new agents that are very effective in inducing apoptosis , differentiation, and/or cell growth arrest in human breast cancer, lung cancer, thoracic cancer, leukemia, and colon cancer cell lines (Giacinti et al., 2006).

2.3 Histone modification inhibitors and breast cancer

As discussed above, histone modification could be used as a novel target for the research of anticancer drugs. So far, several histone modification inhibitors have been developed. HDAC inhibitors are the most studied type of histone modification inhibitor up to now (Tab 3).

It showed that combination of the HDAC inhibitor vorinostat with paclitaxel and bevacizumab could induce a partial or complete response in more than 50% of patients with metastatic breast cancer (Wong, 2009; Jovanovic et al., 2010). In addition, the HDAC inhibitors have different role in ER+ and ER- breast cancer cells. In ER+ cells, HDAC inhibitors reduce the transcriptional level of ER and its response genes, while they

reestablish ER expression in ER- cell lines. But the HDAC inhibitor could potentiate and restore the efficacy of anti-estrogen therapy in preclinical models in either ER+ or ER- breast cancer cells. This has led to the initiation of several clinical trials combining HDAC inhibitors with anti-estrogen therapy (Thomas et al., 2009). LAQ824 is a novel inhibitor of HDAC that shows antineoplastic activity and can activate genes that produce cell cycle arrest. Combination of the LAQ824 and a DNMT inhibitor (decitabine) showed a synergistic (re-)activation of silenced tumor-suppressor genes in human MDA-MB-231 and MCF-7 breast carcinoma cells (Hurtubise et al., 2006).

Class	In vivo preclinical activity	Clinical phase
Carboxylates (short-chain fatty acids)		
PA	Leukemia, glioblastoma	I/II
PB	Prostate, endometrial	I/II
VA	Brain, melanoma	I/II
AN-9	NSCLC, leukemia	I/II
Hydroxamic acids		
SAHA	Lung, prostate, melanoma	I/II
m-Carboxycinnamic acid bishydroxamic acid	Neuroblastoma	
Suberic bishydroxamic acid	Melanoma, sarcoma	
Pyroxamide		I
TSA	Cervical, hepatoma,	
Oxamflatin	Melanoma	
NVP-LAQ824	Colon, multiple myeloma	I
Electrophillic ketones (epoxides)		
TPX		
AOE		

Class	In vivo preclinical activity	Clinical phase
Depudecin		
Cyclic peptides		
Apicidin	Melanoma, leukemia	
FK-228, FR901228	Melanoma, colon, sarcoma, fibrosarcoma, lung, gastric	I/II
Benzamides		
MS-275	Leukemia, colorectal, gastric, pancreatic, lung, ovarian	I/II
CI-994	Colorectal, pancreatic, mammary, prostate, sarcoma, leukemia	I
Other hybrid compounds		
CHAPs	Melanoma, lung, stomach, breast	
Scriptaid		
Tubacin		
JNJ16241199		
A-161906		
6-(3-Chlorophenylureido)caproic hydroxamic acid		
PXD101	Breast, prostate, ovarian, colon, NSCLC	

Table 3. Summary of major HDAC inhibitors (Acharya et al., 2005; Laird, 2005).

3. Conclusion

In summary, Histone modifications provide crucial regulatory functions in the process of gene transcription, and they play very important roles in the proliferation, metastasis, chemotherapy and other aspects of breast cancer, as well as many other human cancers. The reversibility of histone modification makes it could be regarded as one valuable target for

the development of novel anticancer strategies. The understanding of all these epigenetics changes and their contribution to breast cancer might take great progress in the field of diagnosis, prognosis and therapy of breast cancer.

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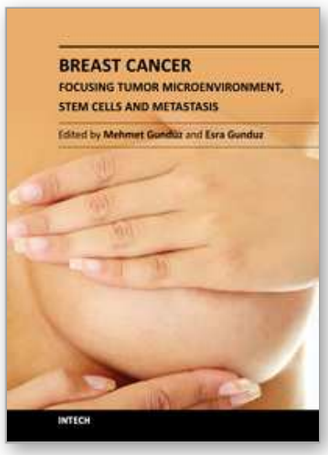

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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed characteristics of breast cancer cell, role of microenvironment, stem cells and metastasis for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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