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REVIEW PAPER

The Histone Acetylation Modifications of Breast Cancer and their Therapeutic Implications

Pingping Guo[1] · Wenqi Chen[1] · Huiyu Li[1] · Meiying Li[1] · Lisha Li[1]

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Abstract
The histone acetylation modifications (HAMs) influence a large number of cellular functions. They are mediated through histone acetyltransferase (HAT) and histone deacetylase (HDAC). Nowadays, people have realized that HAMs are crucial for development and prognosis of breast cancer. Investigations about abnormal HAMs in breast cancer focus on initiating molecular mechanisms in breast cancer development, identification of new biomarkers to predict breast cancer aggressiveness and the therapeutic potential. As HAMs are reversible, breast cancer may be treated by restoring HAMs to normal levels. Indeed, some HDAC inhibitors have been approved by the US Food and Drug Administration to treat certain cancers. Furthermore, HAT inhibitors, HAT activators and HDAC activators may also be used as drugs to treat breast cancer.

Keywords Breast cancer · Histone acetylation · Histone deacetylation · Therapy

Introduction

Breast cancer is one of the most frequent cancers among women, and second only to lung cancer as the leading cause of cancer-related death [1, 2]. Breast cancer can also affect males. Due to delays in diagnosis and estimates, males usually have poorer outcomes [3, 4]. Breast cancer is a heterogeneous disease, consisting of tumors with different pathologic and molecular characteristics, which presents significant challenges for treatment [5, 6]. Classification of breast cancer is currently based on molecular subtypes in order to reflect the hormone-responsiveness of the tumor [7]. According to specific molecular subtypes, breast cancer can be separated into two main classes and four groups (Table 1) [8, 9]. This classification reflects the breast cancer heterogeneity and complexity of diagnosis, prognosis, and treatment [7]. Based on the four-group classification system discussed, breast cancer research has become more and more efficient.

The histone acetylation modifications are controlled by a balance in activity between HAT and HDAC [10, 11]. HATs catalyze the transfer of acetyl group from acetyl-CoA to the amino group of lysine residues and forms ε-N-acetyl lysine, which induces euchromatin structure [12, 13]. HATs can be divided into five families: the p300/CBP family, the GNAT family, the SRC family, the MYST family, and the TAFII250 family, all subfamilies include transcription factor and steroid receptor co-activators with catalytic activity. In human cells, the HAT family mainly includes three subfamilies: the MYST family, the GNAT family, the p300/CBP family [14]. Another class of enzymes, HDACs, can catalyze deacetylation through the hydrolysis of acetyl groups from the lysine residues [11]. HDACs can lead to transcriptional repression and the formation of heterochromatin [15]. Currently, eighteen different isoenzymes of HADCs are known which are divided into four subclasses. ClassI HDACs(HDAC1,HDAC2,HDAC3, and HDAC8) are related to the yeast RPD3 deacetylase, classIHDACs localize almost exclusively to the nucleus and are ubiquitously expressed in many human cell lines and tissues; classII HDACs are categorized into classIIa (HDAC4,HDAC5,HDAC7,and HDAC9) and classIIb (HDAC6 and HDAC10) are homologous to the yeast Hda1 deacetylase, classII HDACs shuttle between the nucleus and cytoplasm with certain cellular signals; and classIII HDACs include seven HDACs(SIRT1 to SIRT7), which show homology with the yeast Sir2 family [16–18].

Although the functional significances of each of histone acetylation modifications have not been fully elucidated,

✉ Lisha Li
43973966@qq.com

[1] The Key Laboratory of Pathobiology, Ministry of Education, Norman Bethune Medical College, Jilin University, Changchun 130021, China

Table 1 Classification of breast cancer on molecular characteristics

Category	Hormone receptor status	Category	HER2 status
Luminal	ER,PR positive	Luminal A	HER2 negative
		Luminal B	HER2 positive
Non-luminal	ER,PR negative	HER2+	HER2 positive
		Triple negative	HER2 negative

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2

many studies have shown that the acetylation of histone is related to gene expression and regulation. Some studies have demonstrated that the aberrant histone acetylation modifications are related to cancer in general, including breast cancer [19]. One common occurrence in cancer is the global reduction of monoacetylated lysine 16 of histone H4 (H4K16), and low levels of H4K16 acetylation is suggested as an early event in breast cancer [19]. Suziki et al. has found that the acetylation level of ac-H4 and ac-H4K12 is decreased in ductal carcinoma in situ and invasive ductal carcinoma compared with the normal breast epithelium [13]. H3K4ac associated with both early and late breast cancer cell phenotypes. Enrichment of H3K4ac is over-represented at promoters of genes associated with cancer-related phenotypic traits, such as estrogen response and epithelial-to-mesenchymal transition pathways [20]. In addition to regulating the expression of tumor suppressor genes and oncogenes, aberrant histone acetylation modifications are also related to the expression of some other genes, including DNA repair, apoptosis, metabolism, metastasis, cellular homeostasis, cell adherence, cell cycle regulation, and cell growth in breast cancer [11, 19]. Altogether, maintenance of the balance of histone acetylation modifications is essential for the regulation of gene expression and the maintenance of the normal status of cells. Since acetylation modifications are reversible, we can maintain a normal level of acetylation modifications to treat breast cancer. HATs/HDACs activators and inhibitors may become potential drugs in treatment of breast cancer, and some HDAC inhibitors are undergoing preclinical and clinical trials [21]. In this review, we will discuss the relationship between histone acetylation modifications and breast cancer. In addition, the potential therapy of breast cancer will be discussed according to histone acetylation modifications mechanisms.

Histone Acetylation and Breast Cancer

There is a very close relationship between histone acetylation and breast cancer, and histone acetylation modifications are very important for the development and treatment of breast cancer. Histone acetylation can alter the electrostatic charge by neutralizing positive charges of histones, because of the DNA is negative, the global acetylation of histone tails could decrease electrostatic interactions between the basic lysine residues and the negatively charged DNA. So it can induce the formation of euchromatin, which becomes more open to provide access for transcription factors bind to DNA easily; and gene transcription become active [12, 13]. Histone acetylation promotes the expression of certain genes, which can cause breast cancer. P300 is a lysine acetyltransferase that catalyzes the attachment of an acetyl group to lysine residues of histones, which leads to some genes activation including several oncogenic. Heightened p300 expression has been observed in primary human breast cancers [22, 23]. Furthermore, histone acetylation also can inhibit breast cancer. P300 could significantly augment the expression of catechol-O-methyltransferase (COMT) gene. COMT is an important metabolic enzyme, which can catalyze the conversion of estrogen and increase the metabolic rate of estrogen. Thus, p300 can promote the expression of COMT gene and reduce the proliferation of MCF-7 breast cancer cells stimulated by estrogen [24].

Histone Deacetylation and Breast Cancer

HAT is a kind of enzyme that can change the structure of the chromatin, its important role in breast cancer is to change the expression of certain genes by altering the structure of the chromatin, leading to the occurrence of tumors. For example, HDAC2, LSD1 (lysine-specific demethylase 1) and SIRT1 are shown to act together in a single compound that represses gene transcription through compression of the chromatin. Derr, R.S., et al. has found that the expression of SIRT1 and LSD1 in normal breast tissue is significantly lower than that in breast cancer tissue. Moreover, the expression levels of the histone-modifying enzymes HDAC2, LSD1 and SIRT1 are correlated with tumor differentiation and tumor cell proliferation [25]. HDAC can inhibit the expression of GABARAPL1, which is autophagy related genes, and promote the production of breast cancer [26]. In regulation of gene expression, HDAC not only can lead to breast cancer, in some cases, it also can inhibit the occurrence of breast cancer. As an important angiogenic factor, vascular endothelial growth factor (VEGF) can promote angiogenesis in a series of pathological conditions, including cancer, inflammation, and ischemic discorders. People have found that transcription factor KLF-4 can recruit HDAC2 and HDAC3 at the VEGF promoter, which will lead

to a decrease in the expression of VEGF, and then inhibition of breast cancer occurs [27]. HDAC can also repress metastasis-associated genes expression, which could significantly suppress breast cancer progression and metastasis [28].

Histone Acetylation Modifications as Therapeutic Targets in Breast Cancer

As we all know, both genetic and epigenetic alterations can control the progression of cancer. Genetic alterations are impossible to reverse, while epigenetic alterations are reversible; so epigenetic alterations have recently come forward as a critical factor for cancer treatment and prognosis. People have found HDAC and HAT inhibitors could potentially represent new options for cancer therapy [12, 13, 29]. Through the above, HATs and HDACs can also inhibit the growth of tumor, the activators of HATs and HDACs also have potential for cancer suppression [30]. We will introduce in detail below.

Treatment of Breast Cancer with Histone Acetyl Transferase Inhibitors

Histone acetyl transferase inhibitor (HATi) can inhibit the activity of HAT, and it can reduce the acetylation levels of histone. According to some research, HATi has the potential to treat cancer, including neuroblastoma [14], glioma [31], lung cancer [32], prostate cancer [33], leukemia, breast cancer and so on [34]. Currently, several different structures of HAT inhibitors have been reported, including bisubstrate inhibitors, natural products and synthetic compounds. According to research, HATi can promote breast cancer cell death by inhibiting DNA repair. HAT Tip60 is a key mediator of the DNA damage response. TH1834 is the inhibitor of Tip60 and it can significantly inhibit Tip60 activity in vitro. People have found that if we treat cells with TH1834, the breast cancer will apoptosis because of unrepaired DNA damage [34]. Garcinol is a HATi, people have found that on treatment with garcinol in MCF-7 cells, estradiol-induced cell apoptosis is increased, cell circle progression is arrested at G0/G1 phase, and the rate of cell proliferation is repressed [35]. HATi will be expected to become new drugs for the treatment of tumors, including breast cancer [12].

Treatment of Breast Cancer with Histone Deacetylase Inhibitors

Histone deacetylase inhibit (HDACi) can block HDAC activity, and it will result in the hyper-acetylation of lysine residues of histone. HDACi as a kind of epigenetic therapy for cancer drugs in the treatment of hematological malignancies has been applied to the clinical investigation [36]. Present studies show that HDACis play an important role in the treatment of breast cancer [37]. HDAC inhibitors chelate the zinc co-enzyme factor, thereby blocking HDACs catalytic activity. According to the functional groups, HDAC inhibitors can be divided into four groups: hydroxamic acids, cyclic tetrapeptides, short chain fatty acids, and benzamides [19, 38]. Some of these HDAC inhibitors have been developed in the treatment of tumor; suberoylanilide hydroxamic acid (SAHA), which was the first approved HDACi for clinical treatment by the FDA [39].

HDAC inhibitors can inhibit breast cancer through a variety of ways and assist in the treatment of breast cancer also play a certain role. HDACi can affect cell mitosis. In inflammatory breast cancer, HDACi CG-1521 can block mitotic spindle formation and prevent abscission during cytokinesis, which leads cells to apoptosis [40]. HDACi can be a function

Table 2 Overview of current some HDAC inhibitors in breast cancer treatment

HDAC inhibitor	Category	Inhibitor of the enzyme or site	Combined with	Mechanism involved of HDAC inhibitor	Stage of study	Condition	Citation
Entinostat	Benzamide	ClassI HDAC	Exemestane	Induce apoptosis by reversing Bcl-2 overexpression	Phase 2	ER+ breast cancer	[45]
			Lapatinib	Induce cells apoptosis by Bim expression	Phase 1	HER2+ breast cancer	[42]
Suberoylanilide hydroxamic acid	hydroxamic acids	Pan-HDAC	Olaparib	Induce the accumulation of DNA DSBs	None	TNBC	[46]
			Ionizing radiation	Enhance DNA damage through the inhibition of DNA repair proteins	None	TNBC, MCF-7	[43]
Sodium butyrate	short chain fatty acids	Inhibit the H4 deacetylation	etoposide	Reduce DSB repair capacity	None	MCF-7	[41]
Abexinostat	Hydroxamic acid	Pan-HDACi	None	Induce cancer stem cells differentiation	None	Breast cancer stem cells	[47]
panobinostat	Hydroxamic acid	Pan-HDACi	Aromatase inhibitor(AI)	Suppress proliferation by suppressing the NF-κB1 pathway	Phase 2	Breast cancer	[48]

MCF-7, estrogen receptor positive breast cancer; T47D, estrogen receptor positive breast cancer; TNBC, triple-negative breast cancer

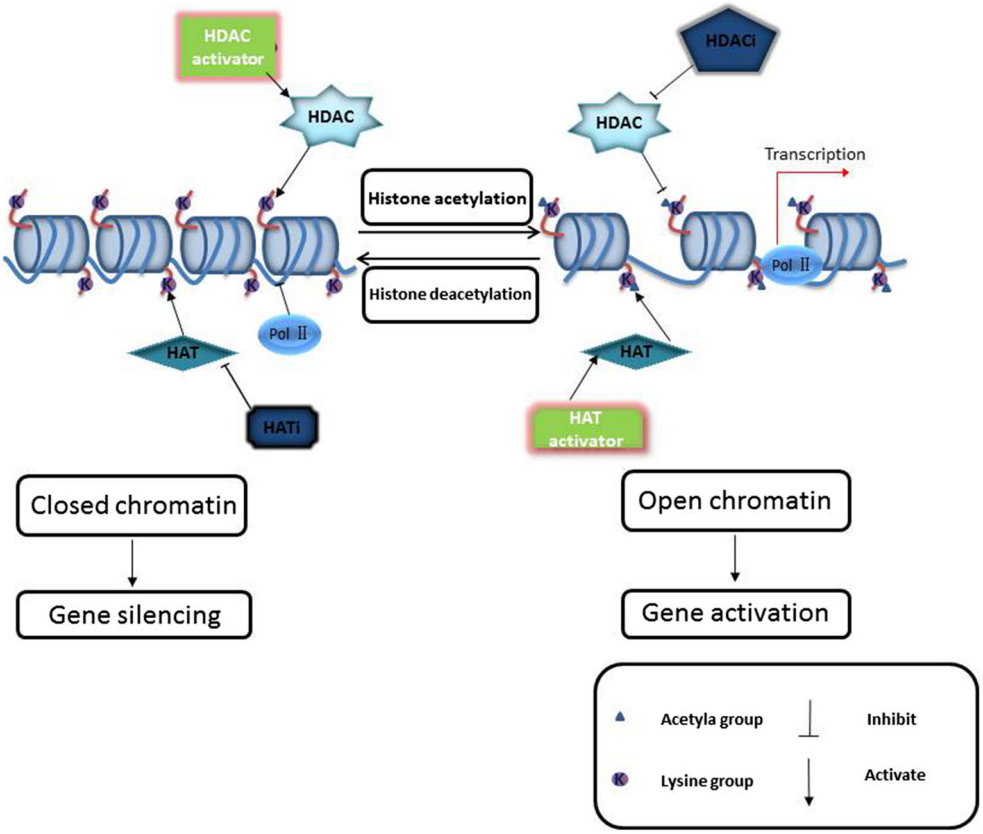

Fig. 1 Regulation of gene transcription by histone acetylation modifications. Histone acetylation is regulated by HDACs and HATs. HATs can make the lysine group of histone tails get acetyla group, which is associated with open chromatin and active transcription. HDACs can remove acetyla group from the lysine group of histone tails, which will lead to chromatin compaction and gene silencing. The activators of HATs and HDACs can promote the HATs and HDACs activity, so the activators of HATs can promote gene transcription and the activators of HDACs can inhibit gene transcription. The inhibitors of HATs and HDACs can inhibit the HATs and HDACs activity, so the inhibitors of HATs can inhibit gene transcription and the inhibitors of HDACs can promote gene transcription

of the DNA repair process, HDACi sodium butyrate can promote MCF-7 cells death by suppressing DNA double strands break repair [41]. In addition to being able to produce an anticancer effect, HDACi can also help other drugs or treatments. For example, HDACi can increase the sensitivity of breast cancer to radiotherapy and chemotherapy [42, 43]. HDACi can also help other drugs to treat breast cancer. For example, oncolytic herpes simplex virus (oHSV) is used for against tumors invasion and metastasis. Even though oHSV have been proved safe in clinical trials, a lack of sufficient potency has slowed the clinical application of this approach. People have found that HDAC inhibitors can enhance the replication

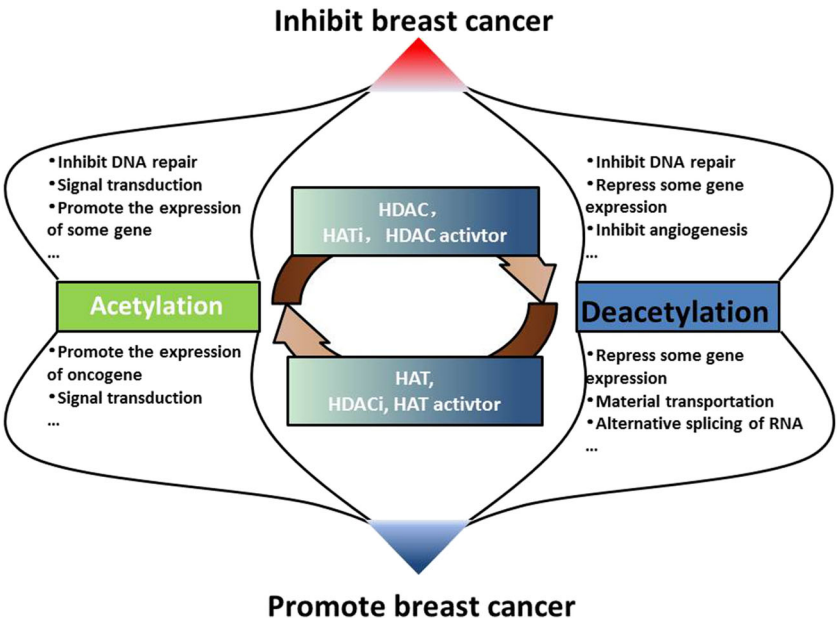

Fig. 2 Acetylation and deacetylation can transform each other and play a role in breast cancer. Acetylation and deacetylation can transform each other. HDAC, HATi, HDAC activator can promote deacetylation; HAT, HDACi, HAT can promote acetylation. Acetylation and deacetylation can promote breast cancer, in some cases, they can inhibit breast cancer

capacity of oHSV in breast cancer and strengthen the effect of oHSV [44]. HDACi can control the expression of some involved in cell cycle, cell proliferation, differentiation and DNA repair genes and play a number of other important roles in the treatment of breast cancer, so it will have good prospects in the treatment of breast cancer. However, in clinical studies, HDAC inhibitors have failed to show very effective antitumor activity as single agents in breast cancer. But HDAC inhibitors have become an attractive of combination regiments for the treatment of breast cancer [45]. An overview of ongoing trials with HDAC inhibitors in breast cancer is provided in Table 2.

Treatment of Breast Cancer with Histone Deacetylase/Acetyltransferase Activator

Histone deacetylase/acetytransferase activator can promote the activity of HDAC/HAT, and can promote/inhibit gene expression (Fig. 1). In addition to the inhibitors of HAT and HDAC, the activators of HAT and HDAC can also become potential treatments for breast cancer. Owing to the growth of breast cancer can be inhibited by the histone acetylation or histone deacetylation [24, 27], the activators of HAT or HDAC may also become drugs for treating breast cancer. Moreover, HAT activators have been studied to treat some diseases, so it is necessary to study the relationship between HAT/HDAC activators and breast cancer. As far as we know, Cholera Toxin B subunit(CTB) is a p300 activator, which can induce breast cancer cell line(MCF-7) apoptosis [49]. Although we know less about histone deacetylase/acetytransferase activators in the treatment of breast cancer, histone deacetylase/acetytransferase activators are likely to become potential method for the treatment of breast cancer.

Conclusion and Outlook

Breast cancer is a significantly heterogeneous disease in histology, genetics and prognosis. Histone acetylation modification is one of the most easy to study and understand epigenetic modifications. We are now very clear that histone acetylation plays an important role in the development of breast cancer. In the past few decades, with the continuous understanding of epigenetic mechanisms, we have understood the molecular mechanisms of breast cancer development. According to the research in the field of epigenetics in particular histone acetylation modifications, acetylation and deacetylation can transform each other, people have found and made some natural and synthetic drugs to maintain intracellular acetylation at normal levels in the treatment of breast cancer, these drugs mainly refers to HATi and HDACi and resume the normal level of acetylation. For example, the FDA approved anticancer drug Farydak, which main ingredient is HDACi panobinostat (LBH589). Meanwhile, HDAC and HAT activator may also be used to treat breast cancer(Fig. 2). In the process of the treatment of breast cancer by histone acetylation modification, we should combine the thought of precision medical. For example, epi-drugs effect locus is different; histone acetylation and deacetylation not only can lead to breast cancer, but also can inhibit the production of breast cancer. This requires us to apply the concept of precision medicine based on the actual situation of patients to use the correct epi-drugs.

Although there are already some drugs that can be applied to clinical practice, people still have to face many problems and have a long way to go. First of all, our understanding of the action of currently known histone acetylation modifications is far from complete; for example, the same modification may lead to different results in different periods of the same tissue. Secondly, most of the experiments we have now are based on the tumor cell line rather than in vivo. Moreover, histone acetylation modifications are reversible, and therefore, epigenetic drugs are needed to continue to use. Next, epigenetic drugs are also likely to have a negative impact. Epigenetic drugs resume normal levels of histone acetylation without specificity and bring side effects. In addition, histone acetylation modifications can lead to breast cancer and can also play a role in inhibiting breast cancer; and epigenetic drugs should be combined with other therapeutic methods to treat breast cancer. These questions are what we have to face. Although we are facing so many problems, but with further research, we can improve our understanding of the effects of histone acetylation modifications on breast cancer, then these issues will be resolved accordingly. In short, It is firmly believed that the study of epigenetic related research will bring the gospel to breast cancer patients.

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Compliance with ethical standards

Conflicts of Interest No potential conflicts of interest to disclose.

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