FEBS Letters 507 (2001) 88–94 FEBS 25346

Dynamic chromatin remodeling on the HER2 promoter in human breast cancer cells

Sandip K. Mishra, Mahitosh Mandal, Abhijit Mazumdar, Rakesh Kumar*

Department of Molecular and Cellular Oncology, Room Y4.6032, University of Texas M.D. Anderson Cancer Center-108, 1515 Holcombe Blvd., Houston, TX 77030, USA

Received 3 September 2001; accepted 13 September 2001

First published online 5 October 2001

Edited by Julio Celis

Abstract Deregulation of the *HER2* oncogene occurs in 30% of human breast cancers and correlates with poor prognosis and increased propensity for metastasis. Since the molecular basis of *HER2* overexpression in human cancers is not known, we sought to determine whether chromatin remodeling pathways are involved in the regulation of *HER2* expression. We report that compared with breast cancer cells expressing a low level of *HER2*, *HER2*-overexpressing breast cancer cells contained significantly higher levels of acetylated and phosphorylated histone H3, and acetylated histone H4 associated with the *HER2* promoter. Decreased recruitment of histone deacetylases in the promoter is also noted in the *HER2*-overexpressing cell. The association of acetylated histone H4 with *HER2* gene chromatin and *HER2* expression in breast cancer cells was upregulated by an inhibitor of histone deacetylases. Treatment with histone deacetylase inhibitor also reduced the association of histone deacetylase-1 and -2 with the *HER2* promoter. In addition, the tumor promoters 12-*O*-tetradecanoylphorbol-13-acetate and okadaic acid stimulated the association of phosphorylated histone H3 on serine 10 with the HER2 promoter and also stimulated *HER2* expression. These findings identify histone acetylation and histone phosphorylation as novel regulatory modifications that target *HER2* gene chromatin, and suggest that elevated levels of these chromatin-relaxing components in the vicinity of the *HER2* gene promoter may constitute an important non-genomic mechanism of *HER2* overexpression in human breast cancer. © 2001 Published by Elsevier Science B.V. on behalf of the Federation of European Biochemical Societies.

Key words: *HER2*; Breast cancer; Chromatin remodeling; Histone acetylation

1. Introduction

Growth factors and their receptors play an essential role in the regulation of mammary epithelial cell proliferation. Abnormalities in the expression and action of receptor tyrosine kinases contribute to the progression and maintenance of the malignant phenotype in breast cancer [1]. For example, the human epidermal growth factor receptor 2 (HER2) has been found to be overexpressed in 20–30% of breast tumors, and is frequently associated with an aggressive clinical course, short disease-free survival periods, poor prognosis, and higher propensity for metastasis in human breast cancer [2]. Overexpression of *HER2* in transgenic mice has been shown to cause breast tumors [3]. Conversely, downregulation of *HER2* inhibits the transformed phenotype in cancer cells and leads to growth inhibition [4–6]. In spite of the widely acknowledged role of *HER2* overexpression in breast cancer, the mechanism of *HER2* overexpression in breast cancer remains elusive.

Following the discovery of HER2 protein upregulation in human cancer, it was generally believed that *HER2* gene amplification was the cause of *HER2* overexpression in cancer cells. However, a number of studies using human breast cancer cell lines have repeatedly demonstrated a role of enhanced transcription in upregulating the net expression of *HER2* mRNA per gene copy [7–9]. This stimulated transcription is presumably due to elevated activity of the transcription factors with consensus sites in the HER2 promoter. In fact, over the years, several transcription factors, including AP-2, PEA3, RBP-Jk, and HTF, have been shown to enhance transcription from the HER2 promoter [10–14] and hence, have been implicated in the process of *HER2* overexpression in cancer cells.

The eukaryotic genome is compacted with histone and other proteins to form chromatin, which consists of repeating units of nucleosomes [15]. For transcription factors to access DNA, the repressive chromatin structure needs to be remodeled. Dynamic alterations in the chromatin structure can facilitate or suppress access of transcription factors to nucleosomal DNA, leading to transcription regulation. One way to achieve dynamic alterations in chromatin structures is through alterations in the acetylation or phosphorylation states or both of nucleosomal histones [15,16]. Acetylation of core histones occurs at lysine residues on the amino-terminal tails of the histones, thus neutralizing the positive charge of the histone tails and decreasing their affinity for DNA. Hyperacetylated chromatin is generally associated with transcriptional activation, whereas hypoacetylated chromatin is associated with transcriptional repression [17–19]. The acetylation state of histones is regulated by a dynamic interaction between recently identified groups of enzymes known as histone acetyltransferases and histone deacetylases (HDACs) [19]. In addition to acetylation, another mechanism that can result in the unfolding of chromatin is phosphorylation of histone H3 [20,21]. In brief, acetylation and phosphorylation constitute important links between chromatin structure and transcription outcome.

Despite the widely acknowledged role of enhanced transcription in *HER2* overexpression, the molecular mechanism

*Corresponding author. Fax: (1)-713-745 3792.
E-mail address: rkumar@mdanderson.org (R. Kumar).

Abbreviations: ChIP, chromatin immunoprecipitation; HER2, human epidermal growth factor receptor 2; TSA, trichostatin A; TPA, 12-*O*-tetradecanoylphorbol-13-acetate

PII: S0014-5793(01)02951-9

by which *HER2* gene chromatin affects the level of *HER2* transcript and the potential role of chromatin remodeling pathways in the non-genomic overexpression of *HER2* in breast cancer cells remains unexplored. Here we explored the hypothesis that histone acetylation and histone phosphorylation regulate HER2 promoter chromatin and, consequently, expression of *HER2* transcript in breast cancer cells. We provide new evidence that elevated levels of chromatin-relaxing components in the vicinity of the *HER2* gene promoter may be responsible for *HER2* overexpression in human breast cancer.

2. Materials and methods

2.1. Cell cultures and reagents

Human breast cancer cells were cultured in the recommended media supplemented with 10% fetal bovine serum. Antibodies against acetylated H3 and acetylated H4 and trichostatin A (TSA) were purchased from Upstate Biotechnology. The anti-acetylated H3 antibody recognizes K9 and K14 [22–24]. The anti-acetylated H4 antibody recognizes tetra-acetylated H4 with high affinity [25,26]. Antibody against phosphorylated histone H3 at serine 10 was from Cell Signaling Technology. Antibodies against HER2, HDAC1 and HDAC2 were from Santa Cruz. Phorbol 12-myristate 13-acetate and okadaic acid were purchased from Gibco BRL.

2.2. Cell extracts and immunoblotting

For preparation of cell extracts, cells were washed three times with phosphate-buffered saline and lysed in buffer (50 mM Tris–HCl, pH 7.5: 120 mM NaCl; 0.5% Nonidet P-40; 100 mM NaF; 200 mM $NaVO_5$, 1 mM phenylmethylsulfonyl fluoride; 10 μg/ml leupeptin; 10 μg/ml aprotinin) for 15 min on ice. The lysates were centrifuged in an Eppendorf centrifuge at 4°C for 15 min. Cell lysates containing equal amounts of protein were resolved on 7% SDS–polyacrylamide gel, transferred to nitrocellulose, and probed with appropriate antibodies.

2.3. Chromatin immunoprecipitation (ChIP) assay

Approximately 10^6 cells were treated with 1% formaldehyde (final concentration, v/v) for 10 min at 37°C to cross-link histones to DNA. The cells were washed twice with phosphate-buffered saline, pH 7.4 containing protease inhibitor cocktail (Boehringer Mannheim). The ChIP assay was performed as described [27,28]. The sequences of the primers used in this study are described in Table 1.

2.4. RT-PCR analysis and HER2 promoter–reporter assays

The sequences of the HER2 primers are described in Table 1. Single-step RT-PCR reaction was carried out in a 50 μl reaction, followed by 35 cycles of 1 min at 94°C, 1 min at 55°C, and 1 min at 72°C and a final cycle of 7 min at 72°C. The RT-PCR product was resolved onto a 1% agarose gel [29]. The HER2 PCR product was 910 bp.

The HER2 promoter–luciferase activity was determined as described after transiently transfecting with pNeulit [30], which contains the HER2 promoter fused with a reporter luciferase gene [12].

3. Results and discussion

3.1. Acetylated histones interact with the HER2 promoter in breast cancer cells

To investigate the potential role of chromatin-remodeling components in the overexpression of *HER2* in human breast cancer, we did ChIP assays to examine the acetylated histone H3 and H4 associated with the *HER2* promoter. We determined the baseline acetylation status of histone H3 and H4 around the PEA3 site in the HER2 promoter. The significance of the PEA3 site in the HER2 promoter was established by mutating the PEA3 site [12], which abolishes the HER2 promoter activity, five-fold in a reporter-based system (data not shown). For these initial studies, we used a series of well-characterized breast cancer cell lines with low (such as

Table 1

Primer pairs 5′-3′ forward/reverse	Name
AACACATCCCCCTCCTTGACTATC AGCTTCACTTTCTCCCTCTCTTCG	ChIP for HER2
CGCGAAGAGAGGGAGAAAGTGA CGATATGTGCATCTGTAAAAGCAATT	ChIP for pNeulit
TTGGACAGCACCTTCTACCG GCAGGAGTTACGTTCTCTGG	HER2 for RT-PCR

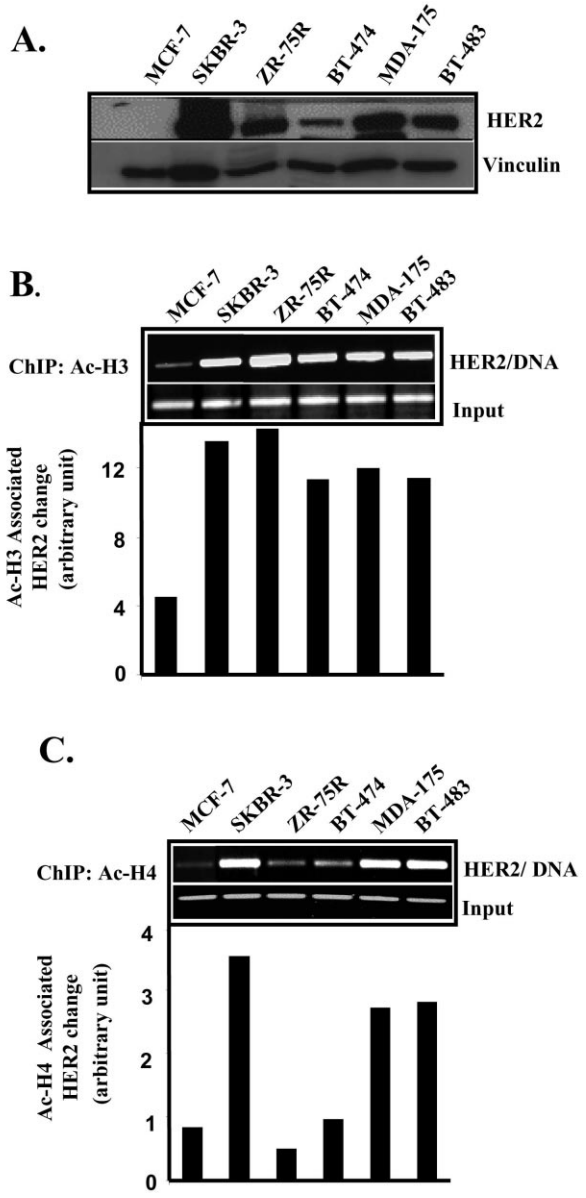

Fig. 1. Acetylation of the HER2 promoter chromatin in *HER2*-overexpressing breast cancer cells. A: Western blot analysis of HER2 protein expression in breast cancer cell lines. B, C: Association of HER2 promoter with acetylated histone H3 and histone H4. Chromatin lysates were immunoprecipitated with antibodies against acetylated histone H3 (B) and acetylated histone H4 (C), and samples were processed as described in Section 2. The upper panels show the PCR analysis of the 313 bp HER2 DNA fragment associated with acetylated histone H3 or acetylated histone H4. The 1% input DNA is shown in the lower panels. Results are presented as quantitation of fold change of acetylated H3/H4-associated HER2/DNA signal with reference to equal input DNA.

MCF-7 cells) or high HER2 content due to gene amplification (SKBR-3 and BT-474 cells [8]) or increased transcription (ZR-75R, MDA-175, and BT-483 cells [8]). Compared with MCF-7 cells, *HER2*-overexpressing breast cancer cells exhibited significantly higher levels of both acetylated histone H3 (Fig. 1B) and acetylated histone H4 (Fig. 1C) associated with the *HER2* promoter. The observation that the extent of histone H3 acetylation of the *HER2* promoter was similar in cells without *HER2* gene amplification (such as ZR-75R cells) and cells with *HER2* amplification (such as SKBR3) suggested that the observed association of acetylated histones with the HER2 promoter in cells with high *HER2* expression might be independent of the status of *HER2* gene amplification. These observations suggested the possibility of preferential targeting of HER2 promoter chromatin by histone acetylation components.

3.2. HDAC inhibitor stimulates association of acetylated histones H3 and H4 with the HER2 promoter

To examine the role of chromatin remodeling via histone acetylation in *HER2* expression, we next evaluated the effect of the HDAC inhibitor TSA on the levels of the HER2 promoter-associated acetylated histones. As shown in Fig. 2A, there was no effect of TSA on the amount of *HER2* promoter interaction with the acetylated histone H3. However, TSA treatment (8 h, 132 nM) resulted in a significant enhancement of *HER2* promoter association with the acetylated histone H4 in several breast cancer cell lines, with a maximum stimulation of this association in the MCF-7 cell line (Fig. 2A). As there is no significant effect of 8 h treatment of MCF-7 cells with 132 nM TSA on the cell cycle analysis by FACScan (Fig. 2C), the observed modulating effect of TSA on the *HER2* gene chromatin was not a consequence of cell cycle effects of TSA.

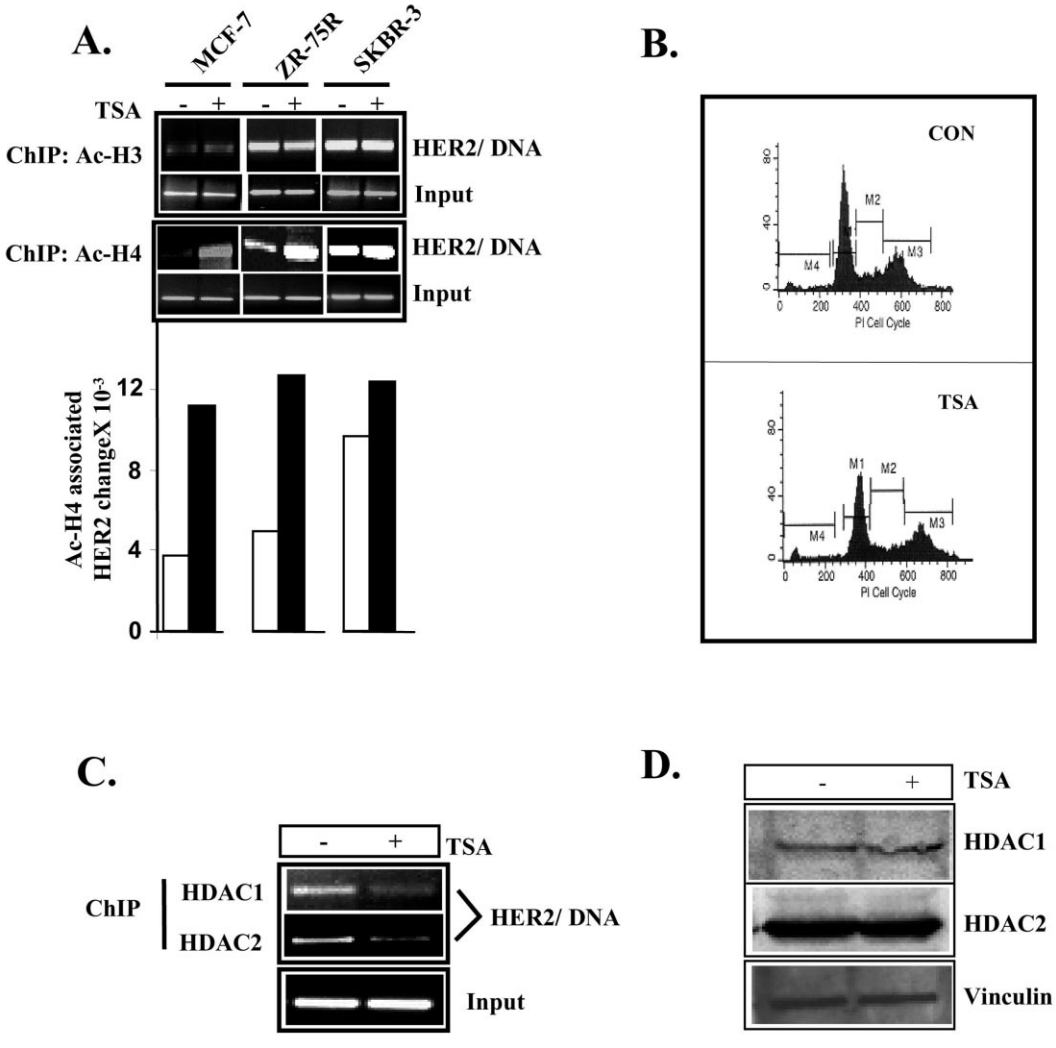

Fig. 2. Stimulation of HER2 gene chromatin interaction with the acetylated histone H4 by HDAC inhibitor. A: MCF-7, ZR-75R and SKBR-3 breast cancer cells were treated with 132 nM TSA for 8 h. Chromatin lysates from control and TSA-treated cells were immunoprecipitated with anti-acetylated histone H3 or anti-acetylated histone antibodies. Levels of the HER2 promoter associated with acetylated histone H3 and histone H4 are shown. B: Cell cycle distribution of control and TSA-treated (132 nM for 8 h) MCF-7 cells. C: Association of HDAC1 and HDAC2 with HER2 promoter chromatin and effect of TSA. Inhibition of HER2 gene chromatin interaction with HDACs by HDAC inhibitor. Chromatin lysates from MCF-7 (treated with or without 132 nM TSA for 8 h) and ZR-75R breast cancer cells were immunoprecipitated with anti-HDAC1 and -HDAC2 antibodies, and levels of associated HER2 promoter are shown. D: Effect of TSA treatment (132 nM for 8 h) on the expression of HDAC1 and HDAC2 in MCF-7 cells.

3.3. TSA promotes dissociation of HDAC1 and HDAC2 from the HER2 promoter

Because TSA promotes histone acetylation by inhibiting HDACs and because HDACs have been shown to interact with the target gene chromatin [31], we explored whether HDACs are recruited around the PEA3 site in the HER2 promoter and if such interactions are affected by TSA. As shown in Fig. 2C, more HDAC1 and HDAC2 are found in MCF-7 cells than in ZR-75 cells. Treatment of MCF-7 cells with TSA resulted in decreased physical interaction of HDAC1 and HDAC2 with the endogenous *HER2* promoter (Fig. 2C). There was no effect of TSA treatment on the expression of HDAC1 and HDAC2 in MCF-7 cells (Fig. 2D).

3.4. HDAC inhibitor stimulates HER2 expression

Since hyperacetylation of target gene chromatin is known to be generally associated with increased transcription [18], we examined the ability of TSA to upregulate *HER2* promoter activity using a HER2–luciferase reporter construct containing the HER2 promoter [12,30]. Inhibition of HDAC activity by TSA stimulated the *HER2* promoter-driven transcription from the reporter system (Fig. 3A). To test whether the transiently expressed *HER2* template is assembled as chromatin, we used a modified ChIP method. MCF-7 cells transfected with HER2–luciferase plasmid were treated with or without TSA. Histone-associated DNA fragments were immunoprecipitated with antibodies against acetylated histone H3 or H4, and amplified by PCR using primers specific for HER2–luciferase (Table 1). As shown in Fig. 3B, transfected HER2–luciferase plasmid was assembled as chromatin and TSA enhanced the association of acetylated histone H4 but not histone H3 with the transiently expressed *HER2* template. This observation is consistent with the finding that TSA affects the levels of acetylated histone H4 associated with the endogenous HER2 promoter (Fig. 2A).

Next we determined the effect of TSA on *HER2* expression

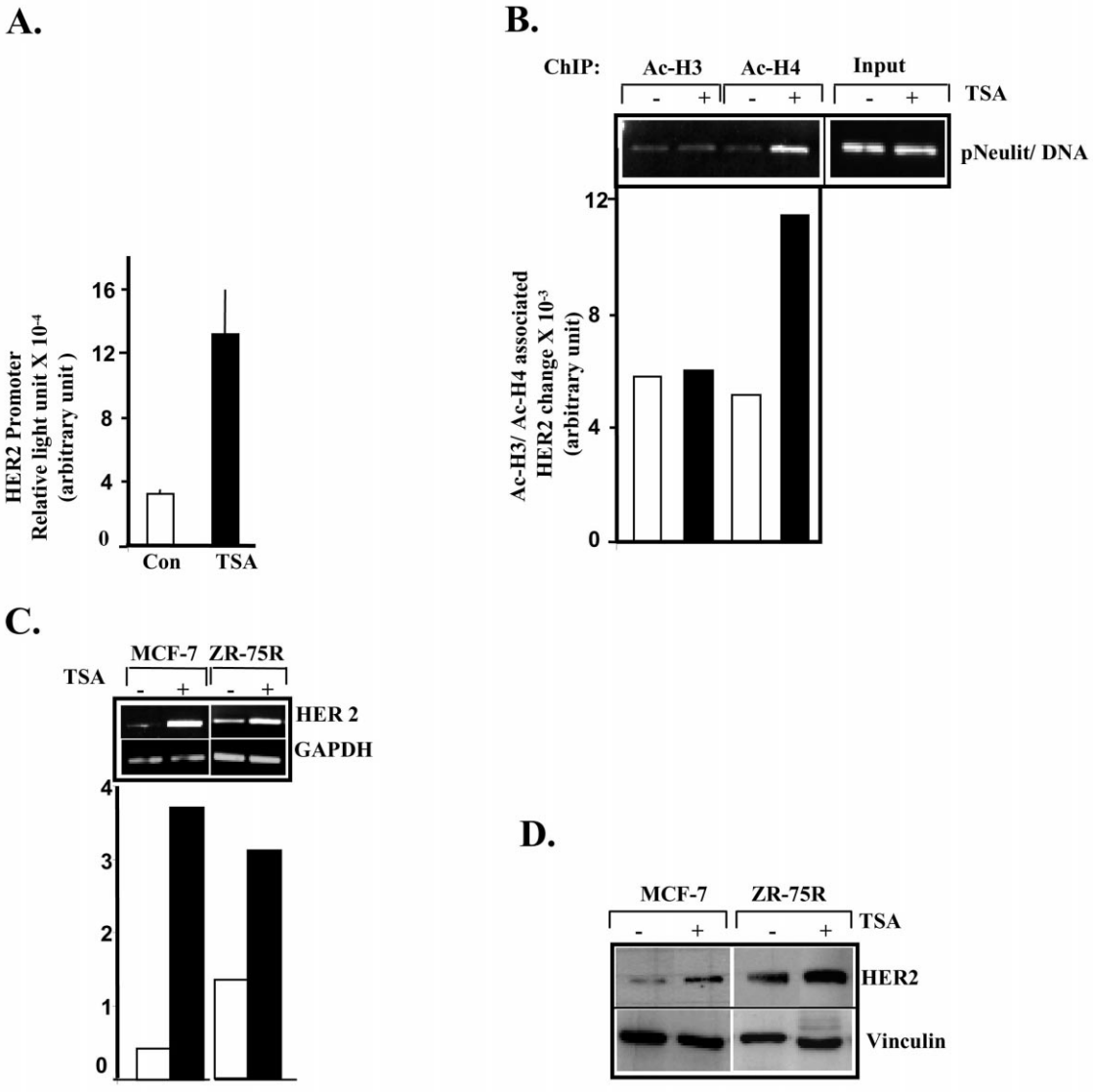

Fig. 3. Stimulation of *HER2* expression by HDAC inhibitor. A: Effect of TSA on HER2 promoter–luciferase in MCF-7 cells. B: Effect of TSA treatment (132 nM for 8 h) on the association of acetylated histone H3 and histone H4 with the HER2 promoter adjacent to transiently expressed luciferase gene in MCF-7 cells. Input for acetylated histone H3 and acetylated histone H4 ChIP analysis is the same. C: MCF-7 and ZR-75R cells were treated with 132 nM of TSA for 8 h and the levels of HER2 and GAPDH mRNA were assayed by RT-PCR. D: MCF-7 and ZR-75R cells were treated with 132 nM of TSA for 8 h and the levels of HER2 and vinculin proteins were assayed by Western blotting.

in MCF-7 cells (low HER2 content) and ZR-75R cells (high HER2 content without gene amplification). Treatment of cells with TSA (132 nM, 8 h) was accompanied by a significant upregulation of *HER2* mRNA in the both cell lines (Fig. 3C). We further noticed that TSA-mediated increased transcription of HER2 promoter leads to an increased *HER2* expression as compared to the HER2 level in untreated control cells (Fig. 3D).

The expression of only 2% of cellular genes has been shown to be modulated by histone acetylation [19]. Our results have identified the *HER2* gene as one of the targets of chromatin remodeling agents such as TSA. Since TSA preferentially in-

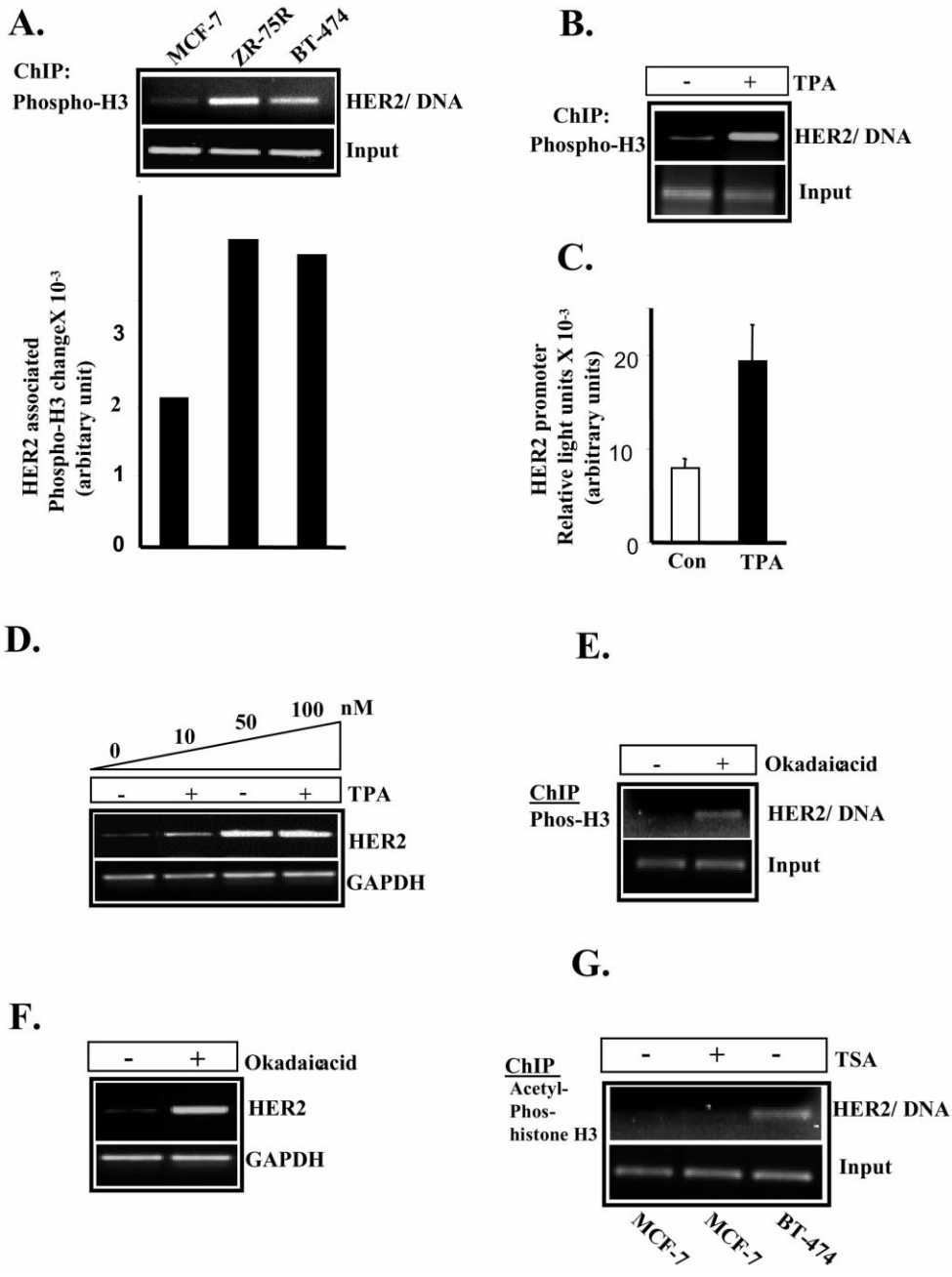

Fig. 4. Remodeling of HER2 promoter chromatin by phosphorylation of histone H3 on serine 10 by TPA. A: ChIP analysis of baseline association of HER2 promoter with phosphorylated histone H3. B: Chromatin lysates from control and TPA-treated (10 nM for 12 h) MCF-7 cells were immunoprecipitated with anti-phospho-histone H3 antibody. The levels of associated HER2 promoter with phosphorylated histone H3 are shown. C: Effect of TPA treatment (10 nM for 12 h) on the levels of HER2 promoter–luciferase in MCF-7 cells. D: Effect of 16 h TPA (10–100 nM) treatment on the levels of HER2 and GAPDH mRNA by RT-PCR assay. E: Remodeling of HER2 promoter chromatin by phosphorylation of histone H3 on serine 10 by okadaic acid and effect of TSA (132 nM) on phospho/acetylated H3 association with HER2 promoter. Chromatin lysates from control and okadaic acid-treated (0.5 μM okadaic acid for 12 h) cells were immunoprecipitated with anti-phospho histone H3 antibody. The levels of associated HER2 promoter are shown. F: Effect of okadaic acid treatment (0.5 μM for 12 h) on the levels of HER2 and GAPDH mRNA by RT-PCR assay. G: ChIP analysis of baseline association of phospho-acetylated histone H3 with HER2 promoter in MCF-7 and BT-474 cell lines and the effect of TSA on it in MCF-7 cells. Chromatin lysates from control and TSA-treated (132 nM for 8 h) cells were immunoprecipitated with anti-acetyl-phospho-histone H3 antibody. The levels of associated HER2 promoter are shown.

duced the status of histone H4 acetylation and its association with the *HER2* promoter chromatin and since TSA activated *HER2* expression, these observations suggest that the acetylation of histone H4 in the vicinity of HER2 promoter chromatin was regulated by HDACs and that histone H4 hyperacetylation remodels chromatin in favor of enhanced transcription activity.

3.5. *HER2 promoter chromatin remodeling by phosphorylation of histone H3 on serine 10*

In addition to acetylation, the second major modification responsible for chromatin relaxation is phosphorylation of histone H3 on serine 10 [20,21]. To explore the potential involvement of histone H3 phosphorylation in *HER2* overexpression in breast cancer cells, we examined the level of HER2 promoter associated with histone H3 in MCF-7 cells (low HER2 content), ZR-75R cells (*HER2* overexpression without gene amplification), and BT-474 cells (*HER2* overexpression due to gene amplification). Compared with MCF-7 cells, both types of *HER2*-overexpressing breast cancer cells exhibited a significant elevation in the amount of HER2 promoter associated with the phosphorylated histone H3 (Fig. 4A). This finding indicates that association of HER2 gene promoter with phosphorylated histone H3 is independent of HER2 gene amplification status. Recent studies have shown that tumor promoters such as phorbol ester 12-*O*-tetradecanoylphorbol-13-acetate (TPA), which acts through protein kinases, regulate cellular mitogenic responses via a common early nucleosomal response leading to chromatin conformational changes due to histone H3 phosphorylation on serine 10 [20]. Because it is not yet fully resolved whether non-genomic pathways can trigger *HER2* overexpression and the process of cellular transformation, and because distinct extracellular signal such as TPA have been shown to contribute to tumorigenesis, we explored whether tumor promoters could influence *HER2* promoter chromatin and *HER2* expression in breast cancer cells. TPA treatment of MCF-7 cells resulted in an increase in *HER2* promoter association with phosphorylated histone H3 (Fig. 4B), activation of HER2 promoter-driven transcription (Fig. 4C), and stimulation of HER2 transcription (Fig. 4D).

Since the process of transformation is also known to be affected by okadaic acid, an inhibitor of serine/threonine protein phosphatase [21], we next examined the effect of okadaic acid on interaction of phosphorylated histone H3 with *HER2* promoter and expression. As illustrated in Fig. 4E, okadaic acid also promoted the interaction of *HER2* promoter with phosphorylated histone H3, and stimulated *HER2* expression (Fig. 4F). Together, these studies led to the notion that histone H3 phosphorylation may constitute an additional mechanism of *HER2* overexpression. Several recent reports have suggested that histone phosphorylation in conjunction with histone acetylation may potentiate gene activation [21], probably by initially loosening the chromatin. In this context we further analyzed the baseline association of acetylated and phosphorylated histone H3 (Lys9Ser10) in the HER2 promoter in MCF-7 and BT474 cells. We found an enhanced association of acetylated and phosphorylated histone H3 with HER2 promoter in BT-474 (high HER2 level) relative to MCF-7 cells (Fig. 4G).

In summary, we found that (1) breast cancer cells with high *HER2* expression exhibited an increased association of acetylated histones H3 and H4 with the HER2 promoter, compared with the cells with low *HER2* expression; (2) association of acetylated histones with the HER2 promoter in high-*HER2*-expressing breast cancer cells was not dependent of the status of *HER2* gene amplification; (3) the promoter is also a target for differential HDAC recruitment and is critically important for H4 acetylation status which in turn influences *HER2* expression; (4) in high-*HER2*-expressing breast cancer cells, HER2 promoter chromatin is also remodeled by phosphorylation of histone H3 on serine 10; and (5) tumor promoters stimulate the association of serine 10-phosphorylated histone H3 with *HER2* promoter and stimulate expression of HER2. These findings identify histone acetylation and histone phosphorylation as novel regulatory modifications that target the *HER2* gene in chromatin and suggest that elevated levels of these chromatin-relaxing components in the vicinity of the *HER2* gene promoter may constitute an important non-genomic mechanism for *HER2* overexpression in human breast cancer.

Acknowledgements: This study was supported by NIH Grants CA80066 and CA65746 and by the Breast Cancer Research Program of the M.D. Anderson Cancer Center (to R.K.). We thank Dr. Mein-Chie Hung for the HER2 promoter constructs.

References

[1] Ullrich, A. and Schlessinger, J. (1990) Cell 61, 203–212.
[2] Slamon, D.J., Godolphin, W., Jones, L.A., Holt, J.A., Wong, S.G., Keith, D.E., Levin, W.J., Stuart, S.G., Udove, J. and Ullrich, A. (1989) Science 244, 707–712.
[3] Bouchard, L., Lamarre, L., Tremblay, P.J. and Jolicoeur, P. (1989) Cell 57, 931–936.
[4] Hudziak, R.M., Lewis, G.D., Winget, M., Fendley, B.M., Shepard, H.M. and Shepard, H.N. (1989) Mol. Cell. Biol. 9, 1165–1172.
[5] Kumar, R., Shepard, H.M. and Mendelsohn, J. (1991) Mol. Cell. Biol. 11, 979–986.
[6] Roh, H., Pippin, J., Boswell, C. and Drebin, J.A. (1998) J. Surg. Res. 77, 85–90.
[7] Kraus, M.H., Popescu, N.C., Amsbaugh, C. and King, C.R. (1987) EMBO J. 6, 605–610.
[8] Hynes, N.E., Greber, H.A., Saurer, S. and Groner, B. (1987) J. Cell. Biochem. 39, 167–173.
[9] Slamon, D.J. and Clark, G.M. (1988) Science 240, 1795–1798.
[10] Bosher, J.M. and Williams, T. (1995) Proc. Natl. Acad. Sci. USA 92, 744–747.
[11] Scott, G.K., Daniel, J.C., Xiong, X., Maki, R.A., Kabat, D. and Benz, C.C. (1994) J. Biol. Chem. 269, 19848–19858.
[12] Xing, X., Wang, S.-C., Xia, W., Zou, Y., Shao, R., Kwong, Y.K., Yu, Z., Zhang, S., Miller, S., Huang, L. and Hung, M.-C. (1999) Nature Med. 6, 189–194.
[13] Chen, Y., Fischer, W.H. and Gill, G.N. (1997) J. Biol. Chem. 272, 14110–14114.
[14] Grooteclaes, M., Vernimmen, D., Plaza, S., Pasleau, F., Hodzic, D. and Winkler-Gol, R. (1999) Cancer Res. 59, 2527–2531.
[15] Owen-Hughes, T. and Workman, J.L. (1994) Crit. Rev. Eukaryot. Gene Express. 4, 403–441.
[16] Felsenfeld, G. (1992) Nature 355, 219–224.
[17] Lee, D.Y., Hayes, J.J., Pruss, D. and Wolffe, A.P. (1993) Cell 72, 73–84.
[18] Vettese-Dadey, M., Grant, P.A., Hebbes, T.R., Crane-Robinson, C., Allis, C.D. and Workman, J.L. (1996) EMBO J. 15, 2508–2518.
[19] Ura, K., Kurumizaka, H., Dimitrov, S., Almouzni, G. and Wolffe, A.P. (1997) EMBO J. 16, 2096–2107.
[20] Mahadevan, L.C., Wills, A. and Barratt, M.J. (1991) Cell 65, 775–783.
[21] Clayton, A.L., Rose, S., Barratt, M.J. and Mahadevan, L.C. (2000) EMBO J. 19, 3714–3726.

[22] Lin, R., Leone, J.W., Cook, R.G. and Allis, C.D. (1989) J. Cell Biol. 108, 1577–1588.
[23] Perry, C.A., Dadd, C.A., Allis, C.D. and Annunziato, A.T. (1993) Biochemistry 32, 13605–13614.
[24] Braunstein, M., Rose, A.B., Holmes, S.G., Allis, C.D. and Broach, J.R. (1993) Genes Dev. 7, 592–604.
[25] Hebbes, T.R., Thorne, A.W. and Crane-Robinson, C. (1988) EMBO J. 7, 1395–1402.
[26] Brownell, J.E. and Allis, C.D. (1995) Proc. Natl. Acad. Sci. USA 92, 6364–6368.
[27] Mazumdar, A., Wang, R.W., Mishra, S.K., Adam, L., Yarmand, R.B., Mandal, M., Vadlamudi, R. and Kumar, R. (2001) Nature Cell Biol. 3, 30–37.
[28] Talukder, A.H., Jorgensen, H.F., Mandal, M., Mishra, S.K., Vadlamudi, R.K., Clark, B.F., Mendelsohn, J. and Kumar, R. (2001) J. Biol. Chem. 276, 5636–5642.
[29] Chan, S.D.H., Antoniucci, D.M., Fok, K.S., Alajoki, M.L., Harkins, R.N., Thompson, S.A. and Wada, H.G. (1995) J. Biol. Chem. 270, 22608–22613.
[30] Miller, S.J., Xing, X., Xi, L. and Hung, M.-C. (1996) DNA Cell Biol. 15, 749–757.
[31] Struhl, K. (1995) Genes Dev. 12, 599–606.