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Potential Prognostic Value of Histone Deacetylase 6 (HDAC6) Combined with Heat Shock Protein 90 (HSP90) in Breast Cancer

유방암에서 히스톤탈아세틸화효소 6 과 열충격단백질 90 의 예후적 가치

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임상의과학과

박 영 희

A thesis of the Degree of Master of Clinical Medical Sciences

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by
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A thesis submitted to the Department of Clinical Medical Science in partial fulfillment of the requirements for the Degree of Master of Science in Clinical Medical Sciences at Seoul National University College of Medicine

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ABSTRACT

Introduction: Histone deacetylase6 (HDAC6) is known as a deacetylase of HSP90 (heat shock protein 90). Many studies have investigated the role of HDAC6 in tumorigenesis and its association with the prognosis of cancer patients. This study aimed to evaluate the prognostic value of HDAC6 and acetylated HSP90 in the cohort of breast cancer patients.

Materials & Methods: The surgical specimens of 291 patients with invasive breast cancer were stained immunohistochemically to assess the expression of HDAC6 and acetylated HSP90 level in addition to the standard pathologic factors. Statistical analyses were performed to evaluate the association of HDAC6, HSP90, and other clinico-pathologic factors, and to find the prognostic values of these factors.

Results: HDAC6 expression and acetylated HSP90 level correlated with HER-2 (human epidermal growth factor receptor-2) amplification. HDAC6 expression correlated with acetylated HSP90 level in the entire patient group (p=0.007). In subgroup analysis, correlation between HDAC6 and acetylated HSP90 level was significant in the HER-2 negative patients (p=0.009), but not in the HER-2 positive patients. HDAC6 expression correlated with acetylated HSP90 level in the ER (estrogen receptor) positive group (p=0.022), but not in the ER negative group. High expression of HDAC6 combined with low acetylated HSP90 level showed the tendency for poorer disease-free survival in the ER positive patients group (p=0.066).

Conclusions: HDAC6 expression and acetylated HSP90 level correlated with each other. High expression of HDAC6 combined with low acetylated HSP90

level had marginal prognostic value for predicting poorer disease-free survival within the ER positive patients group.

Keywords: Histone deacetylase 6, heat shock protein 90, disease-free survival, breast cancer

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INTRODUCTION

Histone deacetylases (HDAC) are a large family of enzymes involved in deacetylation of histone proteins and various cellular proteins such as transcription factors. HDACs are categorized into four classes (I-IV) based on their sequence homology.[1] HDAC6 is a member of class II of HDACs and contains two homologous deacetylase domains which are thought to contribute independently to the overall activity. Unlike other HDACs, HDAC6 is mainly found in cytoplasm and deacetylates non-histone proteins such as α-tubulin, heat shock protein 90 (HSP90), and cortactin. By modulating these proteins, HDAC6 plays an essential role in various cellular processes including cell motility, cell signaling pathways, and cell survival. Recently, it has been shown that HDAC6 is also associated with aggreosome pathway, which eliminates the toxic proteins.[2, 3]

Many studies investigated the association of HDAC6 with various diseases, and the evidence that HDAC6 is involved in processes of malignant transformations is increasing. Thus, HDAC6 is thought to be a putative target of anticancer treatment, and extensive studies involving the HDAC inhibitor have been carried out.[4] In previous research, it was shown that the expression level of HDAC6 is associated with the prognosis of various cancers, especially breast cancer, and that HDAC6 gene is estrogen-responsive.[5, 6]

Heat shock protein 90 (HSP 90), one of the substrates of HDAC6, is a molecular chaperone essential for maintaining the function and conformation

of oncogenic client proteins. Previous studies have shown that aberrant expression of HSP 90 was associated with the prognosis of breast cancer and that the inhibition of HDAC6 led to HSP90 hyperacetylation and inhibition of its functions.[7]

In this study, we evaluated the expression level of HDAC6 in breast cancer specimens and its association with the level of acetylated HSP90. Additionally, the prognostic values of these molecular markers were investigated as well.

MATERIALS AND METHODS

Patients and samples

Invasive breast cancer specimens of 314 patients who had undergone surgical resection at Seoul National University Bundang Hospital between May 2003 and Dec 2006 were collected, and tissue microarrays were constructed as previously described.[8] Twenty-three samples from patients who received neoadjuvant chemotherapy were excluded from this study to eliminate the compounding effect of chemotherapy on pathologic characteristics. The final 291 patients were included in this analysis and the medical records of these patients were reviewed for clinical information. All patients were treated according to the standard treatment guidelines after surgical resection.

Immunohistochemical staining for histone deacetylase 6 (HDAC6), acetylated heat shock protein 90 (HSP90), estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2), Ki-67 proliferation index, and p53 overexpression were prepared, and the results were scored as described in the previous study.[9]

Patients and tumor characteristics are summarized in Table 1. Three male breast cancer patients were included and the median age of diagnosis was 51 years (range 26-87 years). Of 291 patients, 278 (95%) were diagnosed with invasive ductal carcinomas, and 150 patients (51.5%) had low grade (grade 1-2) tumors. One hundred fifty patients (51.5%) had T1 tumors and 154 (52.9%) had no lymph node metastasis. ER and PR were positive in 201 (69.1%) and

168 (57.7%) patients, respectively. HER2 amplification was observed in 51 patients (17.5%).

Statistical methods

The primary endpoint of this study was the disease-free survival (DFS) defined as the time measured from the date of diagnosis to the date of loco-regional recurrence, distant metastasis, or death. DFS was calculated with Kaplan-Meier method, and the differences were verified with log rank test. In multivariate analysis, Cox proportional-hazards model was used to test the independent prognostic value of each variable in multivariate analysis. All statistical analyses were executed with SPSS 21.0.

Table 1. Patient and tumor characteristics

Characteristics		Number	%
Age (years)	Median	50.5	
	Range	26 - 87	
Sex	Male	3	1.0
	Female	288	99.0
Tumor stage	T1	150	51.5
	T2-T4	141	48.5
Nodal stage	N0	154	52.9
	N1-N3	137	47.1
Histology	Invasive ductal	278	95.5
	Invasive lobular	13	4.5
Histologic grade	Grade 1-2	150	51.5
	Grade 3	127	43.6
Estrogen receptor	Negative	90	30.9
	Positive	201	69.1
Progesterone receptor	Negative	123	42.3
	Positive	168	57.7
HER2 amplification	Negative	240	82.5

	Positive	51	17.5
Ki-67 index	≤10%	167	57.4
	>10%	124	42.6
P53 overexpression	Absent	225	77.3
	Present	66	22.7

Abbreviations: HER2 = human epidermal growth factor receptor-2.

RESULTS

The median follow-up duration was 8.49 years (range, 0.5-9.99 years). One hundred eighty-eight patients (64.6%) showed high HDAC6 expression and 95 (32.6%) showed low expression. Acetylated HSP90 was highly expressed in 121 patients, and 157 patients had low acetylated HSP90.

Table 2 shows the correlations of HDAC6 and acetylated HSP90 with other pathologic factors. HDAC6 high expression showed significant association with HER2 amplification (p=0.031). Acetylated HSP90 level was associated with histologic grade, ER positivity, and Ki-67 index (p<0.05). The association between acetylated HSP90 and HER2 amplification showed marginal significance (p=0.089).

The associations between HDAC6 and acetylated HSP 90 are summarized in Table 3. HDAC6 expression was significantly associated with acetylated HSP90 in all patients. In subgroup analysis, the associations of HDAC6 and acetylated HSP90 remained statistically significant in the HER-2 negative and ER positive groups (p<0.05).

The results of the univariate analysis for DFS are summarized in Table 4. Tumor stage was a significant prognostic factor for DFS in all patients, but none of the factors were prognostic in the multivariate analysis. Although HDAC6 was not prognostic in predicting DFS in total ER positive and ER negative patients, as shown in Figure 1, Kaplan-Meier survival curves began to separate after five years according to HDAC6 expression levels in ER positive patients. While there were no events after five years in the HDAC6

low expression group, the disease-free survival probability of HDAC6 high expression groups continued to decline, and this difference in recurrence pattern was also found in ER negative patients.

HSP 90 alone did not show any correlation with DFS in either ER negative or ER positive patients. However, in the subgroup of ER positive patients, HDAC6 high expression combined with low HSP acetylation showed marginal prognostic significance for disease-free survival (Fig. 2, p=0.066).

Table 2. Correlation of pathologic parameters with HDAC6 expression and HSP 90 acetylation

		HDAC 6 expression				Acetylated HSP 90			
		No of patients (%)			*p*- value	No of patients (%)			*p*- value
Characteristics		Total	Low	High		Total	Low	High	
T stage	T1	144	49(34.0)	95 (66.0)	0.900	146	72 (49.3)	74 (50.7)	0.477
	T2-4	139	46 (33.1)	93 (66.9)		136	73 (53.7)	63 (46.3)	
N stage	N0	151	57 (37.7)	94 (62.3)	0.130	148	79 (53.4)	69 (46.6)	0.551
	N1-3	132	38 (28.8)	94 (71.2)		134	66 (49.3)	68 (50.7)	
Histologic grade	G1- G2	143	41 (28.7)	102 (71.3)	0.092	142	58 (40.8)	84 (59.2)	**0.000**
	G3	126	49 (38.9)	77 (61.1)		126	81 (64.3)	45 (35.7)	
Estrogen receptor	Negative	88	27 (30.7)	61 (69.3)	0.587	87	54 (62.1)	33 (37.9)	**0.020**
	Positive	195	68 (34.9)	127 (65.1)		195	91 (46.7)	104 (53.3)	
Progesteron receptor	Negative	121	37 (30.6)	84 (69.4)	0.376	119	65 (54.6)	54 (45.4)	0.399
	Positive	162	58 (35.8)	104 (64.2)		163	80 (49.1)	83 (50.9)	

HER2 amplification	Negative	233	85 (36.5)	148 (63.5)	**0.031**	231	113 (48.9)	118 (51.1)	0.089
	positive	50	10 (20.0)	40 (80.0)		51	32 (62.7)	19 (37.3)	
p53 overexpression	Absent	219	76 (34.7)	143 (65.3)	0.548	218	106 (48.6)	112 (51.4)	0.090
	Present	64	19 (29.7)	45 (70.3)		64	39 (60.9)	25 (39.1)	
Ki 67 index	≤10%	160	57 (35.6)	103 (64.4)	0.447	160	70 (43.8)	90 (56.3)	**0.004**
	>10%	123	38 (30.9)	85 (69.1)		122	78 (61.5)	47 (38.5)	

Abbreviations: HER2 = human epidermal growth factor receptor-2; HDAC = histone deacetylase; HSP = heat shock protein

Table 3. Correlation of HDAC6 and acetylated HSP90

		Number of patients (%)		*p*-value
		Low acetylated HSP90	High acetylated HSP90	
Total	HDAC6 low expression	59 (63.4)	34 (36.6)	**0.007**
	HDAC6 high expression	84 (46.2)	98 (53.8)	
ER (-)	HDAC6 low expression	20 (74.1)	7(25.9)	0.154
	HDAC6 high expression	33 (56.9)	25 (43.1)	
ER (+)	HDAC6 low expression	39 (59.1)	27 (40.9)	**0.022**
	HDAC6 high expression	51 (41.1)	73 (58.9)	
HER2 (-)	HDAC6 low expression	51 (61.4)	32 (38.6)	**0.009**
	HDAC6 high expression	61 (43.0)	81 (57.0)	
HER2 (+)	HDAC6 low expression	8 (80.0)	2 (20.0)	0.282
	HDAC6 high expression	23 (57.5)	17 (42.5)	

Abbreviations: HER2 = human epidermal growth factor receptor-2; HDAC = histone deacetylase; HSP = heat shock protein.

Table 4. Univariate analysis for disease free survival

Characteristics		Mean survival time (year)	*p*-value
Age (years)	≤50	8.64	0.815
	>50	9.10	
Tumor stage	T1	9.25	**0.036**
	T2-T4	8.82	
Nodal stage	N0	9.42	0.057
	N1-N3	8.35	
Histologic grade	Grade 1-2	8.92	0.645
	Grade 3	9.19	
Estrogen receptor	Negative	8.94	0.453
	Positive	9.04	
Progesterone receptor	Negative	8.95	0.311
	Positive	9.09	
HER2 amplification	Negative	9.15	0.907
	Positive	8.56	
Ki-67 index	≤10%	9.12	0.138
	>10%	8.86	
P53 overexpression	Absent	8.98	0.835

	Present	9.03	
HDAC6	Low expression	8.74	0.468
	High expression	9.06	
HSP90 acetylation	Low	8.53	0.210
	High	9.28	

Abbreviations: HER2 = human epidermal growth factor receptor-2; HDAC = histone deacetylase; HSP = heat shock protein.

Figure 1. Kaplan-Meier survival curves for disease free survival of breast cancer patients based on HDAC6 expression in ER negative (A) and ER positive (B) group.

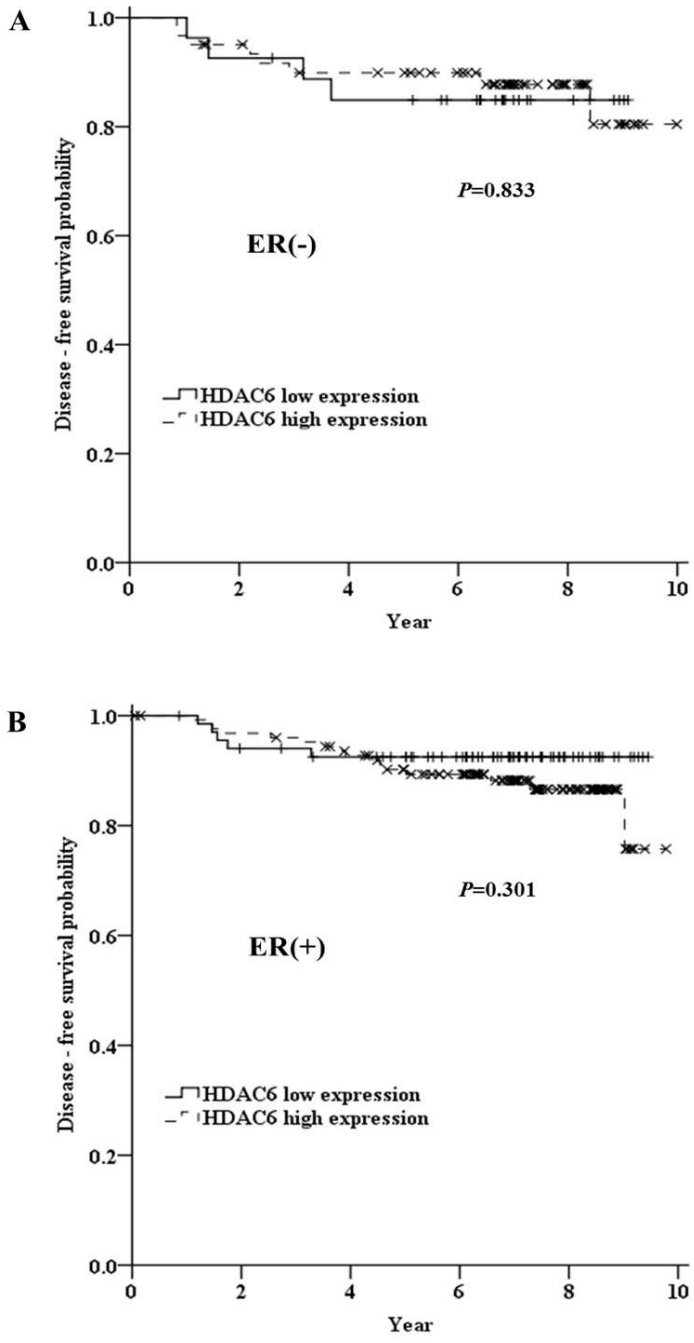
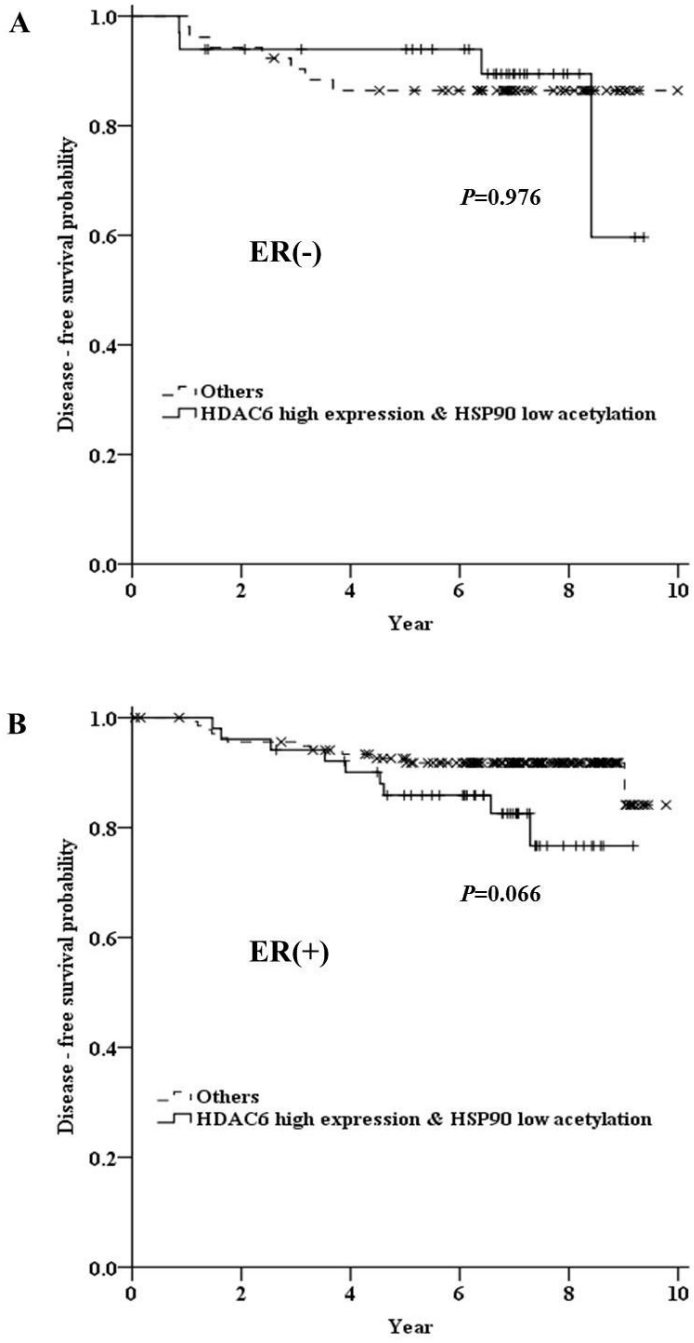


Figure 2. Kaplan-Meier survival curves for disease free survival of breast cancer patients based on HDAC6 expression and HSP acetylation in ER negative (A) and in ER positive (B) group.



DISCUSSION

Many prognostic factors for invasive breast cancer have been identified, and various clinical and pathologic factors, such as age at diagnosis, tumor size, nodal metastasis, histologic grade, estrogen receptor, progesterone receptor, HER-2 amplification, Ki-67 index, and p53 expression levels, are used to predict the prognosis for breast cancer patients. However, prediction of prognosis of patients by these prognostic factors is not perfect, and neither is the treatment outcome. To more accurately predict the prognosis of a patient and to improve the treatment outcome, more studies to understand the molecular events of breast cancer development are needed. Development of new targeted therapy for these molecular markers is expected to improve the treatment outcome of the breast cancer patients.

HDAC6, a member of the HDAC family, is shown to be involved in breast tumorigenesis and thought to be a potential new target of cancer therapy. But the prognostic value of HDAC6 is not yet clearly identified, and the results of previous studies are contradictory. In one study, in ER positive breast cancer, HDAC6 expression was associated with better survival probability and more favorable response to endocrine treatment.[10, 11] The authors concluded that in ER positive patients treated with endocrine therapy, patients with high HDAC6 expression could benefit more from endocrine therapy. Notwithstanding, another study investigated the expression of estrogen-regulated gene, and HDAC6 positive patients showed poorer prognosis than HDAC6 negative patients.[12] Finally, the third study has demonstrated that

ER positive breast cancer cells with high HDAC6 expression showed increased cell motility, which could be interpreted as their having more aggressive features resulting in poorer prognosis.[13]

In this study, the survival graphs of ER positive patients began to separate after five years of follow-up according to the HDAC6 expression level, and late recurrence after five years occurred in only the HDAC6 high expression group. At the same time, the graph of low HDAC 6 expression showed plateau after five years. This is consistent with previous studies reporting that the HDAC6 expression is related to the aggressiveness of cancer and poor prognosis.[12, 13] Thus, HDAC6, in addition to ER positivity, could be used to stratify the prognosis of breast cancer patients more accurately.

And also in ER negative patients, high HDAC6 expression was observed and the late recurrence after 5 years occurred only in these patients. Although HDAC6 is known to be an estrogen-regulated gene, this may suggest that there are cellular pathways that can modulate the HDAC6 expression other than the estrogen-regulated pathway. In other cancers, such as leukemia, lung cancer, and ovarian cancer, those are not known to be involved ER pathways, the associations of high expression of HDAC6 and prognosis of the patients were reported and these support our results.[4, 14-16]

As shown in our previous study, HSP90 expression is known to be associated with prognosis of breast cancer.[9] It is well-known that HSP90 is one of the client proteins of HDAC6. HDAC6 deacetylates HSP90, and when HDAC6 is inhibited, HSP90 becomes acetylated and loses its chaperone function.[17] Based on this, we can postulate that when the HDAC6 expression level is low,

the acetylated HSP90 level will be high. In our results, HDAC6 and acetylated HSP90 expressions were significantly associated, but not in the expected direction. In the HDAC6 low expression group, more patients showed low acetylated HSP90 levels than in the HDAC6 high expression group. There could be several possible explanations for this result. Previous studies evaluated HSP90 acetylation when treated with HDAC6 inhibitor, not basal level of cancer cells. This could mean that it is not the acetylated HSP90 level itself that is important in cancer pathway, but that the change of the HSP acetylation level after malignant transformation could be important for patients' prognosis. To conclude, our result confirmed the close association between HDAC6 and HSP90, although further studies are needed to identify the mechanism of how HDAC6 and HSP90 interact with each other.

In this study, acetylated HSP90 combined with HDAC6 expression showed marginally significant predictive value for disease progression in ER positive patients. Previous studies showed that the high expression of HSP90 in breast cancer was a poor prognostic factor, and HSP90 lost its function when acetylated.[9, 18] This is compatible with our results that patients with low acetylated HSP90 combined with high expression of HDAC6 showed poorer prognosis. This also suggests that using the combination of ER, HDAC6, and HSP90 status, we could more precisely predict the prognosis of breast cancer patients.

HER-2 amplification was associated with HDAC6 expression and showed marginally significant association with acetylated HSP90. HER-2 is one of the client proteins of HSP90, thus downstream signaling pathways from HER-2

are modulated by HSP90. Previous research showed that HER-2 contributed to the carcinogenesis by regulating the HDAC6 expression. Although the signaling pathways involving HDAC6, HSP90, and HER-2 are not yet fully understood, it is evident that these molecules are closely connected and play an essential role in tumorigenesis, and our result confirmed these facts.[19, 20]

In our study, HDAC6, HSP90, and the combination of these factors with any other molecular markers, such as estrogen receptor and HER-2 expression, did not show significant prognostic value in multivariate analysis. Among 291 patients, only 33 (11.3%) patients showed recurrence. While patients who had received neoadjuvant chemotherapy were excluded from the study, relatively early-stage patients were included as a result, and the treatment outcome was good. Therefore, many clinical, pathologic factors such as patient age, histologic grade, hormone receptor status, and HER-2 amplification, known as powerful prognostic factors, were not predictive in our patients due to the low recurrence rate. For the same reason, the prognostic power of HDAC6 and acetylated HSP90 can be underestimated. Therefore, further study involving larger number of patients and with longer follow-up could show the statistically significant prognostic value of HDAC6 and HSP90.

Our study was retrospective and has, therefore, several limitations. First, due to the exclusion of patients with neoadjuvant chemotherapy, we included relatively early-staged patients. Second, there are no standard methods of immunohistochemical staining and scoring systems of HDAC6 and HSP90, and this precludes a straightforward comparison between our results and those obtained in other studies. Despite these limitations, our study suggests that

HDAC6 and HSP90 have prognostic value in breast cancer, so they could become a potential target for the new anticancer treatment.

CONCLUSION

In this study, we demonstrated the relationship of HDAC6, acetylated HSP90, and HER-2 and investigated the prognostic value of HDAC6 and acetylated HSP90 in ER positive patients. Our results contribute to a more accurate prediction of breast cancer prognosis and imply that a new cancer therapy targeting HDAC6 and HSP90 could be implemented in future to improve the treatment outcome of breast cancer.

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국문 초록

서론: 히스톤탈아세틸화효소 6 (HDAC6)은 열충격단백질 90 (HSP90)의 탈아세틸화 효소로 알려져 있다. 이전의 여러 연구에서 HDAC6 가 종양형성과정에 중요한 역할을 할 뿐 아니라 암환자의 예후와 상관관계가 있다는 사실이 밝혀져 있다. 본 연구에서는 유방암 환자에서 HDAC6 과 아세틸화된 HSP90 이 가지는 예후적 가치를 평가하고자 하였다.

방법: 침윤성 유방암으로 진단받은 291 명의 환자들의 수술 검체를 면역조직화학적 염색을 시행하여 기존의 병리학적 요인과 HDAC6 및 아세틸화된 HSP90 의 발현 정도를 확인하였다. HDAC6 및 아세틸화된 HSP90 이 다른 임상적, 병리학적 요인들과 어떤 상관관계를 가지는지를 확인하고 이들의 예후적 가치를 평가하기 위해 통계적 분석을 시행하였다.

결과: HDAC6 과 아세틸화된 HSP90 은 HER-2 (human epidermal growth factor receptor-2)와 각각 상관관계를 보였다. HDAC6 는 아세틸화된 HSP90 와 전체 환자군에서 상관관계를 보였다 (p=0.007). 또한 하위 집단 분석에서 HER-2 음성환자에서는 HDAC6 과 아세틸화된 HSP90 가 유의한 상관관계를 보였으나 HER-2 양성환자에서는 상관관계를 보이지 못하였다. HDAC6 과 아세틸화된 HSP90 의 상관관계는 에스트로겐 수용체 양성환자에서는 유의하였으나 음성환자에서는 상관

관계를 보이지 않았다. 에스트로겐 수용체 양성 그룹에서 HDAC6 의 발현이 높고, 아세틸화된 HSP90 가 낮은 환자의 경우 나머지 환자들보다 더 나쁜 무병 생존율을 보이는 경향성을 보였다 (p=0.066).

결론: HDAC6 와 아세틸화된 HSP90 은 서로 유의한 상관관계를 보였고, HDAC6 의 높은 발현과 아세틸화된 HSP90 의 낮은 발현은 에스트로겐 수용체 양성 환자에서 더 나쁜 무병생존율을 예측할 수 있는 예후적 가치를 가진다.

주요어 : 히스톤탈아세틸화소 6, 열충격단백질 90, 무병 생존율, 유방암

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