Nuclear HDAC6 inhibits invasion by suppressing NF-κB/MMP2 and is inversely correlated with metastasis of non-small cell lung cancer

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ABSTRACT

Histone deacetylase 6 (HDAC6) is a unique member of the histone deacetylase family. Although HDAC6 is mainly localized in the cytoplasm, it can regulate the activities of the transcription factors in the nucleus. However, a correlation of intracellular distribution of HDAC6 with tumor progression is lacking. In this study, we found that a low frequency of nuclear HDAC6-positive cells in tumors was associated with distant metastasis and a worse overall survival in 134 patients with non-small cell lung cancer (NSCLC). Ectopic expression of wild-type HDAC6 promoted migration and invasion of A549 and H661 cells. However, the enforced expression of nuclear export signal-deleted HDAC6 inhibited the invasion but not the migration of both cell lines. The inhibitory effect of nuclear HDAC6 on invasion was mediated by the deacetylation of the p65 subunit of nuclear factor-κB, which decreased its DNA-binding activity to the *MMP2* promoter, leading to the downregulation of MMP2 expression. Our findings indicated that the loss of nuclear HDAC6 may be a potential biomarker for predicting metastasis in patients with NSCLC.

INTRODUCTION

Histone deacetylases (HDACs) regulate the post-translational modification of lysine residues in histone tails by deacetylation, thereby controlling gene expression. HDACs comprise four classes on the basis of their primary homology to the yeast histone deacetylases [1]. HDAC6, which belongs to class IIb, is a unique isoform among HDACs because of its two homologous tandem catalytic domains (all other HDACs have only one) [2, 3]. HDAC6 is predominately expressed in the cytoplasm because its amino acid sequence contains a nuclear export signal (NES) and Ser-Glu-containing tetrapeptide (SE14) [4].

HDAC6 may perform different functions and possess different activities in different cancers [5]. In some human cancers, such as ovarian cancer, HDAC6 is linked to the oncogenic transformation [6]. Aside from solid tumors, HDAC6 is consistently upregulated in primary