Recruitment of histone deacetylases HDAC1 and HDAC2 by the transcriptional repressor ZEB1 downregulates E-cadherin expression in pancreatic cancer.

Pancreatic cancer is characterised by invasive tumour spread and early metastasis formation. During epithelial-mesenchymal transition, loss of the cell adhesion molecule E-cadherin is frequent and can be caused by genetic or epigenetic modifications, recruitment of transcriptional activators/repressors or post-translational modifications. A study was undertaken to investigate how E-cadherin expression in human pancreatic adenocarcinoma and pancreatic cancer cell lines is regulated. In 25 human pancreatic cancer resection specimens, the coding region of the E-cadherin gene (CDH1) was sequenced for somatic mutations. The tumour samples and 11 established human pancreatic cancer cell lines were analysed by immunohistochemistry, western blot analysis, chromatin immunoprecipitation and methylation-specific PCR. The role of specific histone deacetylase inhibitors (HDACi) on pancreatic tumour cell migration and proliferation was studied in vitro. Neither somatic mutations nor CDH1 promoter hypermethylation were found to be responsible for downregulation of E-cadherin in pancreatic cancer. In the transcriptionally active CDH1 promoter, acetylation of histones H3 and H4 was detected whereas HDAC1 and HDAC2 were found attached only
to a silent promoter. Expression of ZEB1, a transcription factor known to recruit HDACs, was seen in E-cadherin-deficient cell lines in which ZEB1/HDAC complexes were found attached to the CDH1 promoter. Moreover, knockdown of ZEB1 prevented HDAC from binding to the CDH1 promoter, resulting in histone acetylation and expression of E-cadherin. HDACi treatment attenuated tumour cell migration and proliferation. These findings imply an important role for histone deacetylation in the downregulation of E-cadherin in human pancreatic cancer. Recruitment of HDACs to the CDH1 promoter is regulated by the transcription factor ZEB1, and inhibition of HDACs may be a promising antitumour therapy for pancreatic cancer.