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Loss of TIMP-3 by promoter methylation of Sp1 binding site promotes metastasis in oral cancer

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The Tissue Inhibitor of Metalloproteinase-3 (TIMP-3) is the only member of the TIMP family that binds to the extracellular matrix and suppresses cancer cell growth, angiogenesis, migration, and invasion. However, whether the abnormal expression and promoter methylation of TIMP-3 facilitates oral cancer metastasis remain unclear. In this study, the DNA methylation levels of TIMP-3 CpG islands were assessed through pyrosequencing. Results showed that the suppression of TIMP-3 transcription by DNA methylation involves the inhibition of the binding of the transcription factor Sp1 to the TIMP-3 promoter as well as the upregulation of DNMT1 and DNMT3B. Functional analyses revealed that TIMP-3 overexpression reduced migration and invasion abilities in oral cancer cells and inhibited lymph node metastasis *in vivo*. Moreover, TIMP-3 regulated epithelial–mesenchymal transition by increasing the expression of the epithelial markers E-cadherin and ZO-1 and reducing the expression of the mesenchymal markers vimentin, fibronectin, Snail and Twist. In conclusion, the results suggested that the suppression of TIMP-3 by DNA methylation contributes to oral cancer metastasis.

Biography

Lin is an associate professor of Institute of Oral Sciences, Chung Shan Medical University, Taiwan. She has received the Ph.D. degree in molecular biology. In particular, her researches have been focused on pharmacology, cancer metastasis, apoptosis and autophagy in oral cancer. She has published more than 40 papers in reputed journals.

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