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Biological Significance of Long Intergenic Noncoding RNA LINC00273 in Lung Cancer Cell Metastasis

Authors : Ipsita Biswas, Arnab Sarkar, Ashikur Rahaman, Gopeswar Mukherjee, Subhrangsu Chatterjee, Shamee Bhattacharjee, Deba Prasad Mandal

Abstract : One of the major reasons for the high mortality rate of lung cancer is the substantial delays in disease detection at late metastatic stages. It is of utmost importance to understand the detailed molecular signaling and detect the molecular markers that can be used for the early diagnosis of cancer. Several studies explored the emerging roles of long noncoding RNAs (lncRNAs) in various cancers as well as lung cancer. A long non-coding RNA LINC00273 was recently discovered to promote cancer cell migration and invasion, and its positive correlation with the pathological stages of metastasis may prove it to be a potential target for inhibiting cancer cell metastasis. Comparing real-time expression of LINC00273 in various human clinical cancer tissue samples with normal tissue samples revealed significantly higher expression in cancer tissues. This long intergenic noncoding RNA was found to be highly expressed in human liver tumor-initiating cells, human gastric adenocarcinoma AGS cell line, as well as human non-small cell lung cancer A549 cell line. SiRNA and shRNA-induced knockdown of LINC00273 in both in vitro and in vivo nude mice significantly subsided AGS and A549 cancer cell migration and invasion. LINC00273 knockdown also reduced TGF-β induced SNAIL, SLUG, VIMENTIN, ZEB1 expression, and metastasis in A549 cells. Plenty of reports have suggested the role of microRNAs of the miR200 family in reversing epithelial to mesenchymal transition (EMT) by inhibiting ZEB transcription factors. In this study, hsa-miR-200a-3p was predicted via IntaRNA-Freiburg RNA tools to be a potential target of LINC00273 with a negative free binding energy of −8.793 kcal/mol, and this interaction was verified as a confirmed target of LINC00273 by RNA pulldown, real-time PCR and luciferase assay. Mechanistically, LINC00273 accelerated TGF-β induced EMT by sponging hsa-miR-200a-3p which in turn liberated ZEB1 and promoted prometastatic functions in A549 cells in vitro as verified by real-time PCR and western blotting. The similar expression patterns of these EMT regulatory pathway molecules, viz. LINC00273, hsa-miR-200a-3p, ZEB1 and TGF-β, were also detected in various clinical samples like breast cancer tissues, oral cancer tissues, lung cancer tissues, etc. Overall, this LINC00273 mediated EMT regulatory signaling can serve as a potential therapeutic target for the prevention of lung cancer metastasis.

Keywords : epithelial to mesenchymal transition, long noncoding RNA, microRNA, non-small-cell lung carcinoma
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