EGFR-L858R mutant enhances lung adenocarcinoma cell invasive ability and promotes malignant pleural effusion formation through activation of the CXCL12-CXCR4 pathway.

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ABSTRACT

Malignant pleural effusion (MPE) is a common clinical problem in non-small cell lung carcinoma (NSCLC) patients; however, the underlying mechanisms are still largely unknown. Recent studies indicate that the frequency of the L858R mutant form of the epidermal growth factor receptor (EGFR-L858R) is higher in lung adenocarcinoma with MPE than in surgically resected specimens, suggesting that lung adenocarcinoma cells harboring this mutation tend to invade the adjacent pleural cavity. The purpose of this study was to clarify the relationship between the EGFR-L858R mutation and cancer cell invasion ability and to investigate the molecular mechanisms involved in the formation of MPE. We found that expression of EGFR-L858R in lung cancer cells resulted in up-regulation of the CXCR4 in association with increased cancer cell invasive ability and MPE formation. Ectopic expression of EGFR-L858R in lung cancer cells acted through activation of ERK signaling pathways to induce the expression of CXCR4. We also indicated that inhibition of CXCR4 with small interfering RNA, neutralizing antibody, or receptor antagonist significantly suppressed the EGFR-L858R-dependent cell invasion. These results suggest that targeting the production of CXCR4 and blocking the CXCL12-CXCR4 pathway might be effective strategies for treating NSCLCs harboring a specific type of EGFR mutation.

Keywords: Lung cancer
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