論 文 要 旨

BHLHE41/DEC2 Expression Induces Autophagic Cell Death in Lung Cancer Cells and is Associated with Favorable Prognosis for Patients with Lung Adenocarcinoma

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Lung cancer constitutes a threat to human health. BHLHE41 plays important roles in circadian rhythm and cell differentiation as a negative regulatory transcription factor. This study investigates the role of BHLHE41 in lung cancer progression. We analyzed BHLHE41 function via in silico and immunohistochemical studies of 177 surgically resected non-small cell lung cancer (NSCLC) samples and 18 early lung squamous cell carcinoma (LUSC) cases. We also examined doxycycline (DOX)-inducible BHLHE41-expressing A549 and H2030 adenocarcinoma cells. BHLHE41 expression was higher in normal lung than in lung adenocarcinoma (LUAD) tissues and was associated with better prognosis for the overall survival (OS) of patients. In total, 15 of 132 LUAD tissues expressed BHLHE41 in normal lung epithelial cells. Staining was mainly observed in adenocarcinoma in situ and the lepidic growth part of invasive cancer tissue. BHLHE41 expression constituted a favorable prognostic factor for OS ($p = 0.049$) and cause-specific survival ($p = 0.042$) in patients with LUAD. During early LUSC, 7 of 18 cases expressed BHLHE41, and this expression was inversely correlated with the depth of invasion. DOX suppressed cell proliferation and increased the autophagy protein LC3, while chloroquine enhanced LC3 accumulation and suppressed cell death. In a xenograft model, DOX suppressed tumor growth. Our results indicate that BHLHE41 expression prevents early lung tumor malignant progression by inducing autophagic cell death in NSCLC.