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DNAJB6A AS TUMOR SUPPRESSOR IN ESOPHAGEAL SQUAMOUS CELL CARCINOMA

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Esophageal squamous cell carcinoma (ESCC) has an especially high incidence in China, with five-year survival rates in Hong Kong being of ~14%. Functional impact and molecular mechanisms of DnaJ (Hsp40) homolog, subfamily B, member 6 (DNAJB6) in ESCC were examined. Tissue microarray (TMA) analysis was performed to investigate the clinical relevance of DNAJB6 in ESCC. In vivo and in vitro functional and molecular studies were performed to verify the TMA results and elucidate the mechanisms for DNAJB6 function. Nuclear but not cytoplasmic DNAJB6 staining was found to correlate significantly with survival in metastasis-free patients by Kaplan-Meier analysis. Expression of nuclear DNAJB6 was down-regulated in tumors compared to normal tissues. In ESCC cell lines, over-expression of the nuclear isoform (DNAJB6a) suppresses in vivo tumor growth in a localization-dependent manner. DNAJB6a over-expression suppresses G1/S transition through inhibiting the key oncogenic Akt signaling pathway and impairs proliferation, by recruiting protein phosphatase 2A through the N-terminal HPD motif. DNAJB6a silencing results in the opposite effect in both cancer cells and immortalized normal esophageal epithelial (NE) cells. DNAJB6a silencing in NE cells also results in senescence-like alterations. DNAJB6a also regulates Akt phosphorylation in other cancers. In summary, nuclear DNAJB6 staining is associated with survival in ESCC patients. DNAJB6a regulates AKT1 phosphorylation in ESCC to suppress tumorigenicity. DNAJB6a may be a useful biomarker for detecting early ESCC tumor initiation and its role in Akt signaling may yet provide opportunities for therapeutic intervention.

Note: This abstract was not presented at the meeting.