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microRNA-17 IS DOWNREGULATED IN ESOPHAGEAL ADENOCARCINOMA CANCER STEM-LIKE CELLS AND PROMOTES A RADIORESISTANT PHENOTYPE

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Esophageal adenocarcinoma (EAC) is an aggressive disease with an extremely poor prognosis. Resistance to neoadjuvant chemoradiation therapy (CRT) remains a critical barrier to the effective treatment of EAC. Cancer stem-like cells (CSC) are a distinct subpopulation of cells implicated in the resistance of tumors to anti-cancer therapy. However, their role in the resistance of EAC to CRT is largely unknown. In this study, using a novel *in vitro* isogenic model of radioresistant EAC, we demonstrate that radioresistant EAC cells have enhanced tumorigenicity *in vivo*, increased expression of CSC-associated markers and enhanced holoclone forming ability. Further investigation identified a subpopulation of CSC that are characterised by high aldehyde dehydrogenase (ALDH) activity, enhanced radioresistance and significantly altered microRNA (miR) expression alterations, including decreased expression of miR-17. *In vitro*, miR-17 overexpression was demonstrated to significantly sensitise radioresistant cells to X-ray radiation and promoted the downregulation of genes with miR-17 binding sites, such as C6orf120. *In vivo*, miR-17 was significantly decreased, whilst C6orf120 was significantly increased, in pre-treatment EAC tumour samples from patients who demonstrated a poor response to neoadjuvant CRT. This study sheds novel insights into the role of CSC in the resistance of EAC to CRT and highlights miR-17 as a potential biomarker of CRT sensitivity and novel therapeutic target in treatment resistant EAC.

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