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MiR-124 induces autophagy-related cell death in cholangiocarcinoma cells through direct targeting of the EZH2–STAT3 signaling axis

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Running title: MiR-124 induces autophagy via EZH2–STAT3 signaling

Abstract

Cholangiocarcinoma (CCA) is a lethal cancer associated with chronic inflammation that has increased in prevalence in recent decades. The dysregulated expression of microRNAs (miRNAs) has been detected in various types of malignancies, and depending on the target genes this can result in miRNAs functioning as tumor suppressors or oncogenes. In this study, we investigated the role of miR-124 in cholangiocarcinoma (CCA) and found that its expression was significantly downregulated in the tumor tissue of patients and in CCA cell lines. Our results provided evidence that miR-124 induces apoptotic cell death and triggers the autophagic flux in CCA cells. EZH2 and STAT3 were identified as direct targets of miR-124. The effect of miR-124 on EZH2 expression in CCA cells was evaluated using cell transfection, xenotransplantation into nude mice and a luciferase reporter assay. Silencing of EZH2 restored the effects of miR-124, whereas overexpression of EZH2 abrogated the effects of miR-124. Silencing of Beclin1 or ATG5 abrogated the effects of miR-124 or siEZH2. *In vivo*, overexpression of miR-124 dramatically induced autophagy-related cell death and suppressed tumorigenicity. Taken together, our findings indicated that downregulation of miR-124 expression was associated

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