Accepted Manuscript

Telomerase reverse transcriptase regulates DNMT3B expression/aberrant DNA methylation phenotype and AKT activation in hepatocellular carcinoma

Jingya Yu, Xiaotian Yuan, Louise Sjöholm, Tiantian Liu, Feng Kong, Tomas J. Ekström, Magnus Björkholm, Dawei Xu

PII: S0304-3835(18)30471-3

DOI: 10.1016/j.canlet.2018.07.013

Reference: CAN 13987

To appear in: *Cancer Letters*

Received Date: 6 May 2018

Revised Date: 29 June 2018

Accepted Date: 7 July 2018

Please cite this article as: J. Yu, X. Yuan, L. Sjöholm, T. Liu, F. Kong, T.J. Ekström, M. Björkholm, D. Xu, Telomerase reverse transcriptase regulates DNMT3B expression/aberrant DNA methylation phenotype and AKT activation in hepatocellular carcinoma, *Cancer Letters* (2018), doi: 10.1016/j.canlet.2018.07.013.

Abstract

Telomerase reverse transcriptase (TERT) acts as a master regulator of cancer hallmarks, but underlying mechanisms remain incompletely understood. We show that TERT is required for the aberrant DNA methyltransferase 3B (DNMT3B) expression and cancer-specific methylation in hepatocellular carcinoma (HCC), through which AKT is activated. TERT depletion inhibited, while its over-expression promoted DNMT3B expression in HCC cells, respectively. Mechanistically, TERT cooperates with the transcription factor Sp1 to stimulate DNMT3B transcription. The tumor suppressors PTEN and RASSF1A were de-repressed following DNMT3B inhibition in TERT-depleted HCC cells. The PTEN promoter analysis demonstrated significantly reduced methylation in these cells. TERT silencing also led to diminished global DNA methylation. The analysis of the Cancer Genome Atlas (TCGA) dataset showed that higher levels of TERT and DNMT3B expression predicted significantly shorter survival in HCC patients. Collectively, our findings establish TERT as an important contributor to cancer-specific DNA methylation and AKT hyperactivation in HCC cells. Given critical roles of both the aberrant DNA methylation and AKT activation in carcinogenesis, this TERT-regulated network or the TERT-DNMT3B-PTEN-AKT axis provides a biological explanation for multi-oncogenic activities of TERT and may be exploited in HCC treatment.