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Commentary

Transcription factor AP-4 (TFAP4) unleashes telomerase reverse transcriptase (TERT) activity in non-viral-associated liver cancers

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Abstract

The mechanisms of transcription factors reactivating TERT in cancers is an active area of research. In this issue, Lim *et al.*, identified TFAP4 directly interacts with TERT causing its reactivation in non-viral-associated liver cancers cell lines, thus uncovering a previously undisclosed function of TFAP-4 in telomere rewiring in liver cancers.

Keywords: TERT; TFAP4; HCC; Telomeres

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The telomerase presents a reverse transcriptase, which elongates telomeres while maintaining genomic integrity [1,2]. It is composed of a catalytic protein unit TERT and a template RNA component, TERC. Recently, cancer-specific somatic mutations driving TERT reactivation were observed in several solid cancers including hepatocellular carcinoma (HCC), the most prevalent forms of liver cancers [3–6]. However, the identities and mechanisms of transcription factors regulating TERT reactivation are not well understood.

In this issue of *Cancer Heterogeneity and Plasticity*, Lim and colleagues report that TFAP4, a member of the basic helix-loop-helix-zipper (bHLH-ZIP) transcription factor family, interacts with TERT causing its reactivation in non-HBV-associated HCC [7]. Using a luciferase reporter assay, the authors expressed several transcription factors which could activate TERT promoter in liver cancer cell lines. Using this approach, TFAP4 was identified as a novel transcription factor whose expression correlated with TERT mRNA in human liver cancer specimens.

Consistent with the notion that cancer cells override telomere shortening events contributing towards unlimited growth potential [8], silencing TFAP4 strongly abrogated TERT mRNA expression and relative telomere copy numbers in liver cancer cell lines.

Direct interactions between transcription factors and TERT are presumed to have functional consequences on TERT activity. Lim *et al.*, addressed this issue by integrating bioinformatic analysis with promoter binding assays to identify four putative binding sites for TFAP4 on the TERT promoter. These were elegantly validated through dual luciferase and chromatin immunoprecipitation assays which confirmed that TFAP4 directly binds to TERT promoter (majorly at −111nt position) to reactivate TERT. Additionally, CCCTC-binding factor (CTCF), a highly conserved zinc finger protein which regulates chromatin structure and gene expression, was identified as a key transcription factor promoting TFAP4 and TERT mRNA expression that subsequently stabilized telomeres.

Chronic alcohol consumption is a well-established risk factor for non-HBV-associated HCC [9]. Based on clinical data, the authors examined the in vitro impacts of alcohol exposure on TFAP-TERT regulatory axis. Indeed, alcohol exposure augmented TFAP4 and TERT mRNA expression in human non-HBV-associated HCC cell lines. Hence, this study highlights TFAP4 as a regulator of TERT reactivation through CTCF in human non-viral-associated HCC, with alcohol exposure exacerbating this process (Figure 1).

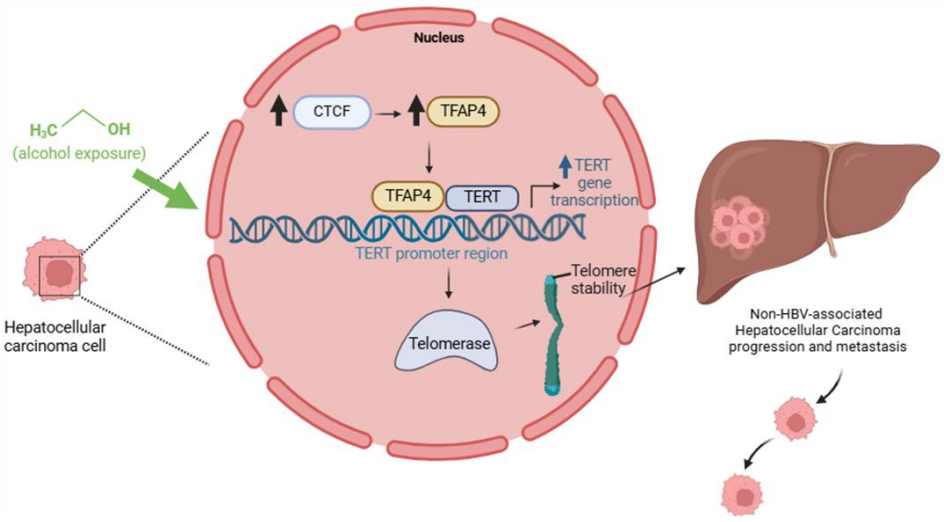

Figure 1. The role of TFAP4 in the reactivation of telomerase reverse transcriptase in non-HBV-associated HCC. Overexpression of CTCF leads to increased transcription of the TFAP4 gene. TFAP4 binds to the TERT promoter at the −111nt, promoting TERT gene transcription. This results in TERT activation and enables the immortalization of hepatocellular cancer cells. Alcohol exposure in non-viral-associated HCC can amplify this process to promote HCC progression and dissemination.

While this study elucidates new mechanistic insights for TERT reactivation, the interplay of additional transcriptional regulators and chromatin assembly factors converging on TFAP4-TERT activity cannot be ruled out. In addition, the role of CTCF in HCC requires in-depth investigations. As such, the specificity and contextual functions of CTCF and TFAP4 in HBV-associated cells should be explored to determine their influence on telomerase activity. From a clinical perspective, it would also be valuable to determine if these transcription factors influence patient outcomes in metabolic dysfunction-associated steatotis liver disease (MASLD)-associated HCC. Lastly, as liver cancers present a complex extracellular matrix rendering a hostile tumor microenvironment [10], the cumulative impact of non-cancerous cell types (including immune cells) in the liver tumor milieu on TERT reactivation through TFAP-4 requires extensive characterization. Taken together, consistent with the notion that TERT promoter activity holds promise as a diagnostic marker for HCC, targeting the TFAP4-TERT interaction is expected to unravel significant therapeutic advantage for HCC treatment.

Competing Interests

The authors have declared that no competing interests exist.

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