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Review Article

Abnormal expression of TFIIIB subunits and RNA Pol III genes is associated with hepatocellular carcinoma☆

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ABSTRACT

The levels of the products of RNA polymerase III-dependent genes (Pol III genes), including tRNAs and 5S rRNA, are elevated in transformed and tumor cells, which potentiate tumorigenesis. TFIIB-related factor 1 (Brf1) is a key transcription factor and specifically regulates the transcription of Pol III genes. *In vivo* and *in vitro* studies have demonstrated that a decrease in Brf1 reduces Pol III gene transcription and is sufficient for inhibiting cell transformation and tumor formation. Emerging evidence indicates that dysregulation of Brf1 and Pol III genes is linked to the development of hepatocellular carcinoma (HCC) in humans and animals. We have reported that Brf1 is overexpressed in human liver cancer patients and that those with high Brf1 levels have shorter survivals. This review summarizes the effects of dysregulation of these genes on HCC and their regulation by signaling pathways and epigenetics. These novel data should help us determine the molecular mechanisms of HCC from a different perspective and guide the development of therapeutic approaches for HCC patients.

1. Introduction

RNA polymerase III (Pol III) mediates the synthesis of a variety of small untranslated RNAs, including 5S rRNA, tRNAs, 7SL RNA, U6 RNA, and Alu-associated microRNAs.[1] These noncoding RNAs are divided into 3 types: 5S rRNA is Type 1, tRNAs are Type 2, and U6 RNA is Type 3.[2]

The products of Pol III-dependent genes (Pol III genes), such as tRNAs and 5S rRNA, are elevated in transformed and tumor cells, suggesting that they are crucial to tumorigenesis. The upregulation of Pol III genes enhances the capacity of cells to synthesize proteins, which is required for cell growth, proliferation, transformation, and tumor development.[3–6]

The promoters of tRNA genes require the transcription factor complexes TFIIIB and TFIIIC, in addition to Pol III (Fig. 1A), for accurate and efficient transcription, whereas the 5S rRNA transcriptional machinery is composed of Pol III, TFIIIA, TFIIIB, and TFIIIC (Fig. 1B). The TFIIIB complex contains three subunits: TATA box-binding protein (TBP), Bdp1, and TFIIB-related factor 1 (Brf1) or Brf2. The TFIIIC complex comprises the TFIIIC 63, TFIIIC 90, and TFIIIC 102 subunits in mammalian cells. Brf1 participates in the regulation of Type 1 (5S rRNA) and Type 2 (tRNAs) gene transcription, whereas Brf2 modulates that of Type 3 genes, such as U6. Studies have indicated that alterations in the activity of the TFIIIB complex are associated with cell transformation and tumorigenesis.[3–6]

TBP is required for transcription by all three nuclear polymerases. TBP combines with TAFs to form at least three distinct complexes—SL1, TFIID, and TFIIIB—which then specify its function in RNA Pol I, II, and III transcription, respectively.[7] In contrast, Brf1 and Bdp1 are used specifically in Pol III gene transcription. Changes in TBP expression alter the cellular levels of Bdp1 but not Brf1,[8] implying that Brf1 is more specific to and critical in the regulation of tRNA and 5S rRNA genes.

2. Dysregulation of Pol III genes promotes cell transformation and HCC

2.1. Oncogenic proteins and tumor suppressors modulate TFIIIB activity to affect Pol III gene transcription

Oncogenic proteins, such as Ras, c-Jun, and c-Myc, stimulate Pol III gene transcription,[5–7,9,10] whereas the tumor suppressors BRCA1,

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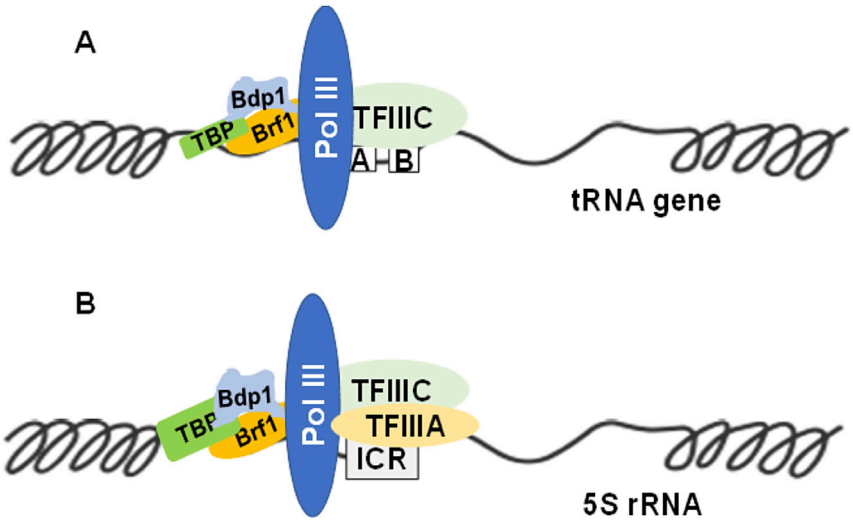

Fig. 1. TFIIIB subunits are recruited to the promoter of Pol III genes. (A) Transcriptional machinery of tRNA genes includes Pol III, TFIIIC, and TFIIIB in the regulatory region of tRNAs. TFIIIB subunits (Brf1, TBP, Bdp1) interact with oncogenic proteins and suppressors. (B) Transcriptional machinery of 5S rRNA has Pol III, TFIIIA, TFIIIC, and TFIIIB in the regulatory region of 5S rRNA. A, B, and ICR are the regulatory elements in the promoter regions of tRNA and 5S rRNA genes. tRNAs and 5S rRNA, the concentrations of which increase in transformed cells and tumor tissues, have important roles in protein synthesis. Abbreviations: Pol III, RNA polymerase III; TBP, TATA box-binding protein; Brf1, TFIIB-related factor 1.

pRb, p53, PTEN, and Maf1 repress transcription of this class of genes.[5,6,9–13] The ability of these oncogenic and tumor suppressor proteins to regulate Pol III gene transcription is attributed to their capacity to control the TFIIIB complex.

Modulation of TFIIIB activity is central in regulating Pol III gene transcription. The tumor suppressors RB and p53 bind directly to TFIIIB and prevent its recruitment to the promoters of Pol III genes.[14–16] PTEN negatively regulates Brf1 phosphorylation and its ability to associate with TBP to form functional TFIIIB complexes.[12] Bdp1 is phosphorylated during mitosis, inducing its selective dissociation from chromatin.[17,18] Maf1 suppresses Pol III gene transcription by repressing TBP expression and inhibiting TFIIIB recruitment to promoters.[19] BRCA1 deficiency increases alcohol-induced Pol III gene transcription, whereas restoration of BRCA1 in cells mitigates this effect.[11] In contrast, cellular and viral oncogenic proteins induce Pol III gene transcription through enhanced expression of individual transcriptional components.

Hepatitis B virus (HBV) is an important cause of the development of HCC in Asia. The HBV oncogenic X protein increases TBP expression, requiring the activation of Ras.[20] Bdp1 expression is induced in cells that are transformed by papovaviruses,[21] whereas a rise in Brf1 mRNA is observed in response to the integration of high-risk human papillomavirus.[22] TBP is upregulated in a clinically significant number of human colon cancers.[23] Overexpression of Brf1 transforms mouse embryo fibroblasts and are in cells of cervical cancers and in biopsies of human HCC cases.[24–26] Our recent studies also indicate that Brf1 is overexpressed in estrogen receptor-positive (ER^+) human breast cancer cases (unpublished).

Alcohol-mediated increases in TBP and Brf1 drive alcohol-induced liver tumor formation.[6] We have demonstrated that Brf1 is overexpressed and tRNA and 5S rRNA transcription is enhanced in human liver cancer patients.[25] Notably, these HCC cases with high Brf1 expression have shorter survivals,[25] suggesting that elevated Brf1 levels reflect the oncogenic status of cells and implicating it as a novel biomarker for HCC.

2.2. Dysregulation of Pol III genes promotes cell transformation and tumor development

Neoplastic cells have increased levels of 5S rRNAs and tRNAs, and a high rate of Pol III gene transcription is a general feature of transformed and tumor cells;[3,4,6,9,25,27–29] thus, regulation of the synthesis of tRNAs and 5S rRNAs is a fundamental determinant of the oncogenic potential of cells. Pol III gene transcriptional products are crucial in tumorigenesis,[24,25,27,28,30] and enhanced Pol III gene transcription is required for oncogenic transformation.[25–31] A decrease in Brf1 reduces Pol III gene transcription, which is sufficient for inhibiting cell transformation and tumor formation in nude mouse.[3–6,27,28]

On consuming alcohol, transgenic animals that express HCV NS5A protein, which present with more advanced fatty liver disease compared with wild-type mice,[32] show greater Pol III gene activity and upregulate TBP and Brf1 versus wild-type animals. In NS5A transgenic mice that form liver tumors,[32] Pol III gene activity is enhanced further.[6] A mechanistic analysis indicates that alcohol increases the cellular levels of c-Jun, which occupies the TBP and Brf1 promoters to enhance TBP and Brf1 expression and Pol III gene transcription.[6] Cases of human HCC with alcohol consumption have higher levels of Brf1 and Pol III gene expression,[25] indicating that alcohol-induced upregulation of these species is critical during the development of HCC.

Alcohol is considered to be carcinogenic in humans by the International Agency for Research on Cancer (IARC).[33,34] Target sites for alcohol-related carcinogenesis in humans include the liver and breast.

It is unknown whether there a common mechanism through which alcohol-associated cancer develops in various human organs. Cytologically, cancer cells consistently show nucleolar hypertrophy, wherein RNA Pol III genes are transcribed.[10] This feature might allow us to identify a shared mechanism of alcohol-associated human cancers by examining the dysregulation of Brf1 and Pol III genes.[3,4,6,25] Animal experiments have shown that alcohol intake promotes tumor development.[35,36] Alcohol increases the expression of Brf1 and Pol III genes in liver and breast cell lines, and the cellular levels of Brf1 in cancer cell lines are higher than in nontumor lines.[3–6,10,25,28,30,37] Thus, alcohol-induced dysregulation of Brf1 and Pol III genes might constitute a common pathway of alcohol-associated cancers,[29] supporting that the induction of Pol III genes contributes to alcohol-associated liver tumor development.

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