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Transcriptional elongation control and HBV cccDNA transcription Recklinghausen's neurofibromatosis

Chengqi Lin
Southeast University, China

Chronic hepatitis B virus (HBV) infection can lead to liver cirrhosis and hepatocellular carcinoma. HBV reactivation during or after chemotherapy is a potentially fatal complication for cancer patients with chronic HBV infection. Transcription of HBV is a critical intermediate step of HBV life cycle. However, factors controlling the HBV transcription remain largely unknown. Here, we found that different P-TEFb complexes are involved in the transcription of the HBV viral genome. Both BRD4 and the Super Elongation Complex (SEC) bind to the HBV genome. The treatment of bromodomain inhibitor JQ1 stimulates HBV transcription and increases the occupancy of BRD4 on the HBV genome, suggesting the bromodomain-independent recruitment of BRD4 to the HBV genome. JQ1 also leads to the increased binding of SEC to the HBV genome and SEC is required for the JQ1 induced HBV transcription. These findings reveal a novel mechanism by which the HBV genome hijacks the host P-TEFb containing complexes to promote its own transcription. Our findings also point out an important clinical implication that is the potential risk of HBV reactivation during therapy with a BRD4 inhibitor, such as JQ1 or its analogues, which is a potential treatment for acute myeloid leukemia.

Figure 1: Transcriptional elongation control of the HBV cccDNA transcription by Super Elongation Complex (SEC) and BRD4.

Recent Publications

1. Wang Y, Shen Y, Dai Q, Yang Q, Zhang Y, Wang X, Xie W, Luo Z and Lin C (2017) A permissive chromatin state regulated by ZFP281-AFF3 in controlling the imprinted Meg3 polycistron. Nucleic Acids Res. 45(3):1177-1185.
2. Luo Z and Lin C (2016) Enhancer, epigenetics and human diseases. Curr Opin Genet Dev. 36:27-33.
3. Luo Z, Lin C, Ashley RW, Bartom E, Gao X, Smith E, and Shilatifard A (2016) Regulation of imprinted gene expression by allele-specific enhancer activity. Genes Dev 30(1):92-101.
4. Lin C, Garrus AS, Luo Z, Guo F and Shilatifard A (2013) The RNA Pol II elongation factor Ell3 marks enhancers in ES cells and primes future gene activation. Cell. 152(1-2):144-56.
5. Luo Z, Lin C, Guest E, Garrett AS, Mohaghegh N, Swanson S, Marshall S, Florens L, Washburn MP and Shilatifard A (2012) The super elongation complex family of RNA polymerase II elongation factors: gene target specificity and transcriptional output. Mol Cell Biol. 32(13):2608-17.

Biography

Chengqi Lin has obtained his PhD degree in Molecular and Cell biology from Stowers Institute for Medical Research in 2013. In 2013, he was awarded an IMCB Junior Investigator (IJI) position to conduct independent research at IMCB, A*STAR, Singapore. In 2017, he became Professor in Southeast University in China. He identified the Super Elongation Complex (SEC) and characterized its essential roles in development and leukemogenesis. He also found that the transcriptional elongation factor Ell3 could serve as a unique epigenetic marker by bookmarking the inactive enhancers of genes for future activation during early development or as early as in germ cells. Recently, his work indicated an essential role of transcriptional elongation control in HBV pathogenesis.

cqlin@seu.edu.cn

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