Alcohol-induced histone H3 phosphorylation mediates RNA Pol III gene transcription

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ABSTRACT
Alcohol has been classified as carcinogenic in humans by IARC. Target sites for alcohol-related carcinogenesis include the breast, liver and multiple additional organs. Is there a common mechanism, which mediates alcohol-associated cancer development in different organs? Cancer cells have a consistent cytological feature of nucleolar hypertrophy, where RNA Pol III (polymerase-dependent) genes are transcribed. This feature provides the possibility to explore a common mechanism of alcohol-associated human cancers by determining the effect of alcohol on the deregulation of **Brf1** (TFIIB-related factor 1) and **Pol III genes** (RNA polymerase III-dependent genes). To investigate this phenomenon, we are currently focusing our studies on alcohol-associated **breast and liver cancers**. Our studies have demonstrated that alcohol-induced deregulation of Brf1 and Pol III genes to promote transformation of liver and breast cells. Brf1 is a specific transcription factor of Pol III genes. Inhibition of Brf1 decreases Pol III gene transcription, which is sufficient for repressing cell transformation and tumor formation. Signaling analysis shows that alcohol strongly induces activation of MSK1 （mitogen and stress activated kinase 1） and H3ph (histone H3 phosphorylation). We have demonstrated that MSK1 mediates H3ph, whereas inhibition of MSK1 by tis specific inhibitor, SB 747651A, inhibits alcohol-induced H3ph. Blocking MSK1 signaling by this inhibitor significantly decreases Brf1 expression and Pol III gene transcription of liver and breast cancer cells. Inhibition of H3S28ph by mutant version of H3, H3S28A attenuates the induction of Brf1 and Pol III genes caused by alcohol. Further studies indicate that H3S28ph occupies the promoters of Brf1 to modulate its expression. Blocking H3S28ph represses cell transformation. These results indicate that alcohol induces H3ph, which mediates Brf1 expression to upregulate Pol III gene transcription, resulting in an increase in cell transformation. Summarily, our studies suggest that alcohol increases Brf1 expression and RNA Pol III transcription through MSK1 and H3ph, which may play a critical role in alcohol-induced tumor development.
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