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Role of epigenetic regulation by histone H3 phosphorylation in non-coding RNA, tRNA transcription of breast cancer

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Non-coding RNAs include rRNAs, tRNAs and small RNAs. Most of small RNAs are derived from cleaved tRNAs called as tRFs (tRNA-derived fragments). tRFs are abundant and have been implicated in stress responses, cancer and neurological disorders. Alcohol has been classified as carcinogenic in humans by IARC. Target sites for alcohol-related carcinogenesis include the breast, liver and multiple additional organs. Our early studies have demonstrated that Brf1 expression and tRNA transcription are increased in alcohol-induced liver tumor. We reported that alcohol activated MAP kinases, JNK1 to upregulate Brf1 expression and tRNA transcription in ER+ MCF-7 cells. MSK1 is a component of MAP kinase downstream. MSK1 mediates H3ph (histone H3 phosphorylation). Thus, we hypothesize that alcohol-induces H3ph modulates tRNA transcription to promote breast cancer development through MSK1. Here, we report that alcohol markedly activates MSK1 and induces H3ph in MCF-7 cells. Inhibition of MSK1 signal attenuates Brf1 expression and decreases in tRNA transcription. Repression of Brf1 expression decreases alcohol-induced colony formation. Alcohol increases occupancy of Brf1 to tRNA gene promoters. Brf1 is overexpressed in the ER+ cases of breast cancer patients. Tamoxifen inhibits Brf1 expression and tRNA transcription. High expression of Brf1 displays longer overall survival period after Tamoxifen treatment. Blocking H3ph represses tRNA transcription. H3ph and Brf1 colocalize in nucleus of the biopsy. Together, these studies demonstrate that alcohol activates MSK1 and induces epigenetic modification, H3ph to enhance Brf1 expression and tRNA transcription, which may play a critical role in alcohol-induced cell transformation and alcohol-associated breast cancer.