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TARGETING HEAT SHOCK PROTEIN 90 ALTERS EPIGENETIC GENES IN ALCOHOLIC LIVER DISEASE

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Abstract -

Chronic alcohol induces acetylation and methylation of chromatin-associated histones that influence transcriptional activity of genes. Molecular chaperone heat shock protein 90 (hsp90) is being recognized as mediator of chromatin remodeling and is upregulated in alcoholic liver disease. We hypothesize that hsp90 plays a pivotal role in altered expression of chromatin modifying enzymes during alcoholic liver injury. To test our hypotheses, C57Bl/6 mice were fed Lieber-deCarli diet with 5% v/v ethanol for 10 days followed by a binge containing 20%v/v alcohol. A single injection of hsp90 inhibitor, 17-DMAG [17-Dimethylamino-ethylamino-17-demethoxygeldanamycin] was administered (30-50 mg/kg BW) i.p. before the binge. Epigenetic PCR array analyzing chromatin modifying enzyme expression was employed to determine effect of chronic alcohol and 17-DMAG treatment. Elevated ALT, triglycerides and steatosis confirmed alcoholic liver injury. Results show significant up-regulation of 5 genes including, ATF2 ($p=0.0003$), a transcription factor with histone acetyltransferase activity, PRMT6 ($p=0.0001$) and SETD7 ($p=0.002$), protein methyltransferases, RPS6KA3 ($p=4.4 \times 10^{-6}$) kinase and HDAC3 ($p=0.0001$) whereas HDAC9 ($p=0.002$) was decreased in alcoholic whole livers. Further, ATF2 was exclusively up-regulated in Kupffer cells (KCs) while PRMT6 increased in alcoholic hepatocytes. HDAC3, SETD7 and RPS6KA3 were increased in both, alcoholic KCs and hepatocytes. HDAC9 was exclusively down regulated in alcohol exposed hepatocytes but not in KCs. Inhibition of hsp90 by 17-DMAG after chronic alcohol exposure alleviated liver injury as noted by significantly lowered serum ALT, TBARS and liver triglycerides. Interestingly, 17-DMAG treatment prevented upregulation of ATF2 ($p=3.13 \times 10^{-5}$), PRMT6 ($p=0.001$) and HDAC3 ($p=0.001$) and inhibited down regulation of HDAC9 ($p=2.6 \times 10^{-8}$) without any effect on expression of SETD7 and RPS6KA3 genes in liver. In summary, our data indicate that chronic alcohol exposure regulates chromatin modifying epigenetic genes in a cell-specific manner likely via molecular chaperone, hsp90. Inhibition of hsp90 leads to modulation of chromatin modifying enzymes with resolution of liver injury. (Supported by the NIH/NIAAA # AA179086)