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Signal transduction pathways in alcoholic liver disease.

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About the Study

Alcoholic Liver Disease (ALD) continues to be a leading cause of disease and fatality in the world, affecting millions of people each year. The liver is the primary organ in charge of ethanol metabolism. The oxidation of ethanol to acetaldehyde is the most common pathway for ethanol metabolism. The course of ALD is well-known, and it encompasses a wide range of liver disorders, from metabolic derangement through inflammation and necrosis (steatohepatitis), fibrosis and cirrhosis, and, in some cases, hepatocellular carcinoma. Alcohol use raises the risk of ALD in a dose- and time-dependent manner [1]. Even strong drinkers, however, only a small percentage get the severe form of the disease, implying that other environmental e.g., cigarette smoking, obesity or genetic e.g., gender or polymorphisms in critical genes factors play a role in overall risk. The signal transduction mechanisms that underpin these processes are still a work in progress. The principal pathways implicated in the action of alcohol and its metabolites, as well as the development of liver disorders which are the Mitogen Activated Protein Kinase (MAPK) family and transcription factors Nuclear Factor-kB (NF-kB) and Activating Protein-1 (AP-1) [2]. These signaling-related route barriers will be discussed briefly.

Mitogen-Activated Protein Kinases (MAPKs) are multifunctional proteins which have been implicated in lipid metabolism control. The effects of alcohol on p42/44 Mitogen-Activated Protein Kinase (MAPK), p38 Mitogen-Activated Protein Kinase (p38 MAPK), and c-Jun N-terminal Kinase (JNK) in normal and regenerated rat liver were studied to better understand the mechanisms by which alcohol reduces hepatocyte proliferation. The activation of p42/44 MAPK and p38 MAPK produced by various agonists was extended when rat hepatocytes were treated with 100 mM alcohol *in vitro* for 16 hours. Agonist-induced JNK activation was not potentiated or prolonged by this therapy. Pertussis toxin prevented alcohol from potentiating p42/44 MAPK activation. Chronic alcohol consumption, on the other hand, suppressed the activation of p42/44 MAPK, p38 MAPK, and JNK produced by partial hepatectomy or different agonists *in vivo*. Acute and chronic ethanol, on the other hand, suppressed hepatocyte proliferation triggered by insulin and epidermal growth factor. Under both conditions, a selective inhibitor of p42/44 MAPK somewhat reversed the inhibition of hepatocyte proliferation caused by acute, but not chronic, alcohol exposure, whereas a specific inhibitor of p38 MAPK further decreased hepatocyte proliferation. These findings show that ethanol inhibits hepatocyte growth in two ways: acute and chronic. Acute alcohol may limit hepatocyte proliferation by inhibiting p38 MAPK activation, but chronic alcohol may inhibit hepatocyte proliferation by inhibiting p42/44 MAPK activation [3].

NF-κB regulates a variety of tasks in distinct cellular compartments, including hepatocyte survival, Kupffer cell inflammation, and HSC survival, inflammation, and activation. Because of its extensive functionality, NF-κB plays a key role in the regulation of central features of chronic liver disease, as well as the wound-healing responses that decide the final outcome. Hepatitis (liver infection by Helicobacter, viral hepatitis caused by HBV and HCV), liver fibrosis and cirrhosis, and hepatocellular cancer are all disorders that involve the NF-κB signalling system. Moreover, the NF-B signalling pathway could be a target for hepatoprotective drug development. Selected Oestrogen Receptor Modulators (SERMs), antioxidants, proteasome inhibitors, IKK inhibitors, and nucleic acid-based decoys have been found to decrease NF-B activity at various degrees and may be effective in the treatment of liver illnesses. NF-B, on the other hand, has an important hepatoprotective function that must be considered when developing new therapeutic regimens [4,5].

Transcription factors AP-1 are homodimers and heterodimers composed of basic region-leucine Zipper (hZIP) protein that belongs to the Jun (C, B, D types), Fos (C,B and 1, 2 types), Jun Dimerization Partners (JDP1, JDP2). AP-1 proteins have as target genes regulating cell proliferation and death. In humans, the c-Jun amino-terminal Kinase (JNK) family of MAP kinases governs cell life and death by regulating the production and activity of cell cycle modulators such as cyclin D1 and p53.Tumor suppressor p53 is an important target for AP-1 effects on

cell life and death. The cell requires ERK1/2- and PKC/PKD dependent signaling mechanisms to sufficiently down-regulate AP-1 to resist to death from superoxide. The existence of countless routes may represent the importance of oxidative stress-damaged cells being eliminated by the organism. In disease states, disruption of either pathway may make hepatocytes more susceptible to oxidative stress death, and efforts to up-regulate these signal transduction pathways could help them survive [6].

Conclusion

Since its discovery more than 20 years ago, the activation of MAPK pathways, after acute or chronic ethanol exposure, can profoundly alter cellular adaptations to its environment. These developments now necessitate defining the importance of MAPK cascade in the molecular actions of ethanol and its patho-physiological consequences on cellular systems. Future also waits targeting of the components of MAPK grid to develop mechanism-based therapeutic tools useful for alcohol related health problems. The NF-κB pathway has emerged as one of the best-characterized signalling pathways. The NF-κB signalling pathway has become one of the well-studied signalling pathways. The key function of NF-κB in liver metabolism is extremely important in chronic liver disorders. Despite a large number of fundamental research investigations and an increasing number of pharmacologic compounds targeting this pathway, there is still a gap in translating these results into clinical hepatology.

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