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Meeting abstract

Role of mesenchymal liver cells in mediating hepatic toxicity and carcinogenesis

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Mesenchymal liver cells (Kupffer cells, KC; sinusendothelial cells, EC) are considered to play a role in the response of the liver to pro-inflammatory stimuli. We studied whether genotoxic and non-genotxic carcinogens are also capable to activate these mesenchymal liver cells. Liver cell suspensions were separated into hepatocytes, KC and EC. Cells were incubated with lipopolysaccharid (LPS), the genotoxic N-nitrosomorpholine (NNM) or non-genotoxic carcinogens like nafenopin, cyproterone acetate, phenobarbital, or arsenic. LPS and NNM incuced a release of TNF-α and superoxide while the other compounds showed mostly minor effects on KC and EC. To assess the impact of activated mesenchymal cells on hepatocarcinogenesis a co-culture model of unaltered and preneoplastic hepatocytes was used. DNA synthesis was significantly higher in preneoplastic than unaltered cells and was further increased by supernatant of LPS-stimulated KC and EC. The supernatant effect was greatly abrogated by antisera neutralizing heparin-binding epidermal growth factor-like growth factor (HB-EGF). HB-EGF itself was a potent inducer of DNA synthesis and mitosis preferentially in the preneoplastic hepatocytes. In conclusion, KC and EC, activated by pro-inflammatory stimuli, may contribute to carcinogenesis via release of growth factors for preneoplastic hepatocytes. Whether this cell activation may be caused by non-genotoxic carcinogens requires further investigations.