2017

Alcoholic Liver Diseases, Stem Cell Disorder and Hepatocellular Carcinoma

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High alcohol consumption is a leading cause of chronic liver diseases, ranging from steatosis, steatohepatitis, cirrhosis and hepatocellular carcinoma (HCC), with lower than an 11% five-year survival for advanced cases. The underlying mechanisms that associated with progression of alcoholic liver diseases (ALD) toward HCC remains poorly delineated. We found that more than half of β2SP-null mouse embryos develop a spontaneous fetal alcohol syndrome–like phenotype, which becomes exacerbated upon exposure to alcohol. Analysis of β2SP-null cells indicates a marked defect in DNA repair in response to various exogenous mutagens including aldehyde. β2SP/Smad3 directly regulates the transcription of Fancd2 both in vivo and in vitro. Liver progenitor/stem cells are observed along the pericentral vein early in regeneration, and later at the portal tracts. Oct4 and Nanog are observed to label cells as early as the first 1-3 weeks, representing early liver regeneration. The putative progenitor cells carry stem cell markers and TGF-β markers - TGFBRII and β2SP. Importantly, we found β2SP in cells at the portal tract structure and Smad4 labels bile duct region of human regenerating liver after 6 weeks. These regions are enriched with liver stem or progenitor cells. We demonstrate that TGF-β induces chromatin insulator CTCF, which facilitates TGF-β–mediated repression of TERT transcription via interactions with β2SP/Smad3. This regulation is abrogated in TGF-β defective mice, resulting in TERT overexpression. The results show that activation of the Smad3/β2SP/CTCF complex on TERT promoter is dependent on TGF-β signaling. Overall, our findings provide new insight into how disruption of the TGF-β pathway correlates alcoholic disease, DNA damage repair and the genomic instability that drives HCC.