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2. **Title**

   Influences of Smoking on Hepatic Progenitor Cell-Mediated Regeneration of Fibrotic Liver

3. **Period**

   2016-2019

4. **Summary**

   The liver is well known to possess highly regenerating potential, but this ability is impaired in the cirrhotic liver. Smoking is recognized as a risk factor for the progression of liver fibrosis. However, the underlying mechanisms, as well as its influence on fibrotic liver regeneration, are virtually unknown. Hepatic progenitor cells (HPCs) have been implicated as a source of hepatocytes in regeneration of fibrotic liver. The purpose of the present study is to examine the influences of cigarette smoking on HPC induction in fibrotic liver.

   We have previously shown that Jagged1 expressed in activated hepatic stellate cells (HSCs) in fibrotic liver induces dedifferentiation of hepatocytes (HXs) into alpha-fetoprotein (AFP)-positive HPCs via Notch2 receptor expressed on the HX surface. Exposure of mice with carbon tetrachloride-induced liver fibrosis to cigarette smoke accelerated hepatic fibrosis, but it did not stimulate the compensatory HPC mobilization. Addition of tobacco extracts into co-culture media of HXs/HSCs inhibited Jagged1/Notch2 signaling and suppressed the dedifferentiation of mature hepatocytes into AFP-expressing HPCs in vitro. We have identified acetaldehyde and isoprene as the tobacco components that inhibit Jagged1 expression in activated HSCs.