Knockout mouse model for human liver cancer

Published date: Feb. 1, 2012

Technology description

Summary

Mitotic spindle checkpoint is a multi-protein network that ensures the equal segregation of chromosomes into two daughter cells during mitosis. One important component of the spindle checkpoint is MAD2 (Mitotic arrest deficient 2), whose abnormal expression has been found in human cancers. MAD2 is located on human chromosome 4q arm, which is often found to be lost in human hepatocellular carcinoma. Further more, the loss of chromosome 4q arm has been found to be associated with p53 mutations in human hepatocellular carcinomas.
The line of conditional compound knockout mice of Mad2 and p53 is generated using the liver-specific albumin gene promoter to drive the expression of Cre-recombinase in liver. The single conditional Mad2 knockout mice were bred with transgenic mice which expresses albumin promoter mediated Cre to obtain liver specific Mad2 knockout mice. The liver specific Mad2 knockout mice were then bred with the single conditional p53 knockout mice to obtain liver specific double knockout mice.
Detail histological analysis by hematoxylin and eosin staining has shown extensive regeneration nodules and bile duct hyperplasia as well as inflammation in both Mad2 single knockout mice and Mad2 p53 double knockout mice. The proliferation of hepatocytes was evaluated by immunohistochemical assay with antibody to Ki67, which is a cellular marker for proliferation. The expression of pro-inflammatory mediators in liver was analyzed by real time RT-PCR.
The liver pathology developed in stages. The disease progressed from enlarged hepatocytes, necrosis and inflammation to nodular regeneration and bile duct proliferation. Up-regulation of several pro-inflammatory cytokines was found in the liver of Mad2-deleted mice. Remarkably, loss of Mad2 in those mice results in hepatocellular adenoma (benign liver tumor) and hepatocellular carcinoma in 60% of animals, which is much higher than only 25% of normal mice with adenoma. The onset of tumor in those transgenic mice is also much earlier than in normal mice (age of 8 months compared with age of 23 months). Furthermore, Mad2 deletion synergize with p53 deletion to cause malignant liver cancers in mice. Array CGH (Comparative Genomic Hybridization) shows that the liver cancers are highly aneuploid.

Advantages

While most hepatocytes in healthy liver are resting cells, deletion of Mad2 in liver activates the cell cycles and causes proliferation of hepatocytes. Cre-mediated, simultaneous liver-specific knockout of Mad2 and p53 induces mouse cancer which share many common features of human liver cancer. These mouse cancers arise spontaneously within a background of regenerative nodules and cirrhosis without hepatotoxic and/or carcinogenic agents.

The cancer develops in stages from liver cell proliferation, fibrosis, regeneration, adenoma to malignant carcinoma, mimicking the development of human liver cancers. The cancers in this mouse model arise spontaneously without the need of hepatoxin and or carcinogens in contrast with most current mouse models of HCC (Hepatocellular Carcinoma), which depend on the administration of hepatotoxic and/or carcinogenic agents to recreate the injury-fibrosis-malignancy cycles.

Mad2 and p53 compound liver specific knockout mice exhibit distinct phenotypes that closely mimic the common features of human hepatocellular carcinoma, which include hepatocyte regeneration, genomic instability and the fibrotic tumor microenvironment.

Institution

Harvard University

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com