Non-viral FoxM1 gene delivery to hepatocytes enhances liver repopulation

Under a research project supported by the National Natural Science Foundation of China (Grant Nos. 30801115, 31271474 and 81471948) and National Key Basic Research and Development Program of China (Grant No. 2011CB966200), Prof. He Zhiying and colleagues from the Second Military Medical University published their research findings entitled "Non-viral FoxM1 gene delivery to hepatocytes enhances liver repopulation" in *Cell Death and Disease* (2014, 5: e1252).

Hepatocyte transplantation has been investigated as a substitute strategy of orthotopic liver transplantation for the treatment of end-stage liver diseases. Several technical hurdles, however, must be removed before the therapeutic liver repopulation, e. g. the insufficient expansion of transplanted hepatocytes in recipient livers. In this study, Prof. He's team found an efficient method to genetically modify primary hepatocytes by non-viral vector delivery. They analyzed the application of FoxM1, a cell-cycle regulator, in enhancing the proliferation capacity of hepatocytes. The non-viral sleeping beauty (SB) transposon vectors carrying FoxM1 gene were constructed for delivering FoxM1 into the hepatocytes *in vitro* and *in vivo*. In comparison with wild-type (WT) hepatocytes, the hepatocytes with FoxM1 were expressed at a higher proliferation rate *in vitro* and an enhanced level of liver repopulation in the recipient livers of both sub-acute injury (fumaryl acetoacetate hydrolase deficient, $Fah^{-/-}$) and acute injury (2/3 partial hepatectomy) mice models. More importantly, no increased risk of tumorigenicity with FoxM1 expression was observed in the recipients even after serial transplantation.

This study suggested that up-regulating FoxM1 expression in hepatocytes by the non-viral SB vector might be a viable approach to promote therapeutic repopulation after hepatocyte transplantation, which could become a potential clinical application. This method could also be used to modify other hepatic cells, such as hepatocytes derived from ES/iPS cells, hepatocytes or hepatic stem cells trans-differentiated from other kinds of cells, which are under study for the future applications of cell transplantation therapy.

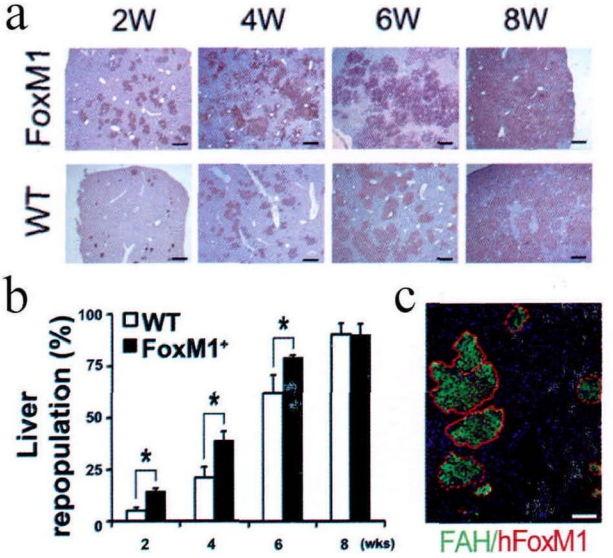

Figure FoxM1-overexpressing hepatocytes modified with non-viral vector possess enhanced capacity of liver repopulation. a and b, Liver repopulations were detected by calculating the ratio of FAH^+ area in whole liver sections 2, 4, 6 and 8 weeks after the transplantation of 2×10^5 $FoxM1^+$ or WT hepatocytes. c, Transfected hepatocytes *in vitro* were transplanted into $Fah^{-/-}$ mice. Six weeks after transplantation, liver tissues of recipients were harvested for anti-FAH and anti-FoxM1 IHF (solid lines: FAH^+FoxM1^+ nodules; dotted line: FAH^+FoxM1^- nodules).