Chromatin remodeling regulates multiple liver functions

Liver is a one of the largest tissues that has the ability to regenerate itself upon stimulation. The liver also performs a variety of complex functions which support body homeostasis including detoxification and providing essential molecules to the blood. Disorganization of liver functions is one of the main characteristics of several severe diseases such as liver cancer and Non-Alcoholic Fatty Liver Disease (NAFLD). Understanding of the mechanisms which control functions of the healthy liver is highly important for development of approaches for treatments of liver diseases. A liver

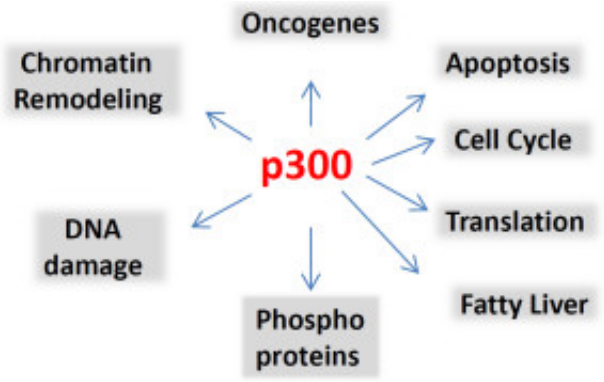

Fig. 1. List of signaling pathways that are controlled by p300.

which is dormant and not regenerating expresses certain genes which determine the biology of the liver and regulate critical biological processes. These genes include a number of liver specific transcription factor, housekeeping genes, genes that control morphology of the liver and many other genes. Given this complexity of gene expression, we aim to understand how the liver changes patterns of gene expression during development of diseases and after challenges.

During the last decade it has become clear that alterations of chromatin structure are key steps in the regulation of the normal liver and during development of disease. It has been shown that there are proteins which work as chromatin remodeling factors by modifying histones and opening or closing DNA for transcription. Among these proteins, histone acetyltransferase p300 has been implicated in the regulation of liver biology; however, molecular mechanisms of this regulation have not been elucidated. We have recently determined these mechanisms using transgenic mice which express a dominant negative p300 molecule, dnp300 mice. This animal model is an excellent tool for the examination of the role of p300 since activities of the endogenous p300 are inhibited in these mice. An examination of global changes in expression of genes in livers of dnp300 mice revealed that p300 regulates multiple pathways. These pathways include chromatin remodeling, DNA damage, fatty liver, oncogenes, apoptosis, cell cycle and translation (Fig. 1). Further

examination of the responses of dnp300 mice to challenges emphasized the significance of these changes in gene expression.

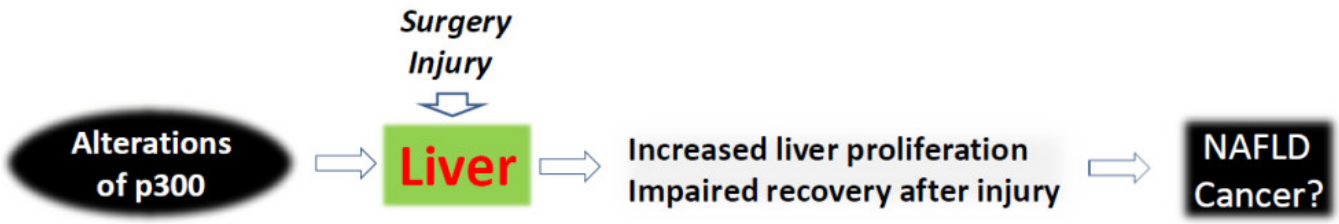

Fig. 2. Alterations of p300 activity might be involved in development of liver diseases.

The liver is a unique tissue which is able to regenerate after massive surgical resections. To examine if p300 is essential for liver regeneration after surgery, we have applied a 2/3 partial hepatectomy model. In this approach, 70% of the liver is removed and the remaining portion starts proliferation and restores to the original size. We found that the inhibition of p300 dramatically increases liver regeneration after surgery and that this process involves additional alterations in the gene expression. The liver is also the main organ which performs detoxification if there is liver injury by chemicals. To determine the role of p300 in liver injury after chemical exposure, we treated WT and dnp300 mice with carbon tetrachloride (CCl_4) and found that the inhibition of p300 blocks the response of the liver to CCl_4-mediated injury. These studies demonstrate that p300 is a key protein which regulates liver responses to surgery and to injury. Our data also shows that alterations of p300 activities might be associated with the development of NAFLD and liver cancer (Fig. 2).

Publication

p300 Regulates Liver Functions by Controlling p53 and C/EBP Family Proteins through Multiple Signaling Pathways.
Breaux M, Lewis K, Valanejad L, Iakova P, Chen F, Mo Q, Medrano E, Timchenko L, Timchenko N.
Mol Cell Biol. 2015 Sep 1