Drug induced liver injury (acute or chronic) followed by regeneration is a well established model system to study the mechanism and cascade of events involved in the process of liver regeneration. Remarkable feature about the liver regeneration is the ability of fully differentiated hepatocytes to take over all metabolic functions, thus maintaining homeostasis. The compensatory phenomenon of regeneration can be accomplished by the division of existing hepatocytes (hepatocyte-driven regeneration) whereas chronic injury involves division and differentiation of an intrahepatic liver progenitor cells into functional hepatocytes (the liver progenitor cell-driven regeneration).

Regeneration of liver is the result of molecular interplay, which is regulated at the level of gene expression at different stages. The expression of gene is tightly regulated through different levels of transcription and translation. Transcriptional regulation involves the “switch on” and “switch off” status of genes. This transcriptional state of “ON” and “OFF” is regulated at the level of chromatin and various other post translational modification of the histones, which can be constitutively explained in terms of epigenetic mechanisms. The epigenetic regulatory mechanisms involve chromatin remodelling, modification of histones and histone variants, DNA methylation and regulation by non-coding RNA. The most widely studied covalent histone modifications are acetylation, methylation, phosphorylation, and ADP-ribosylation. There are several molecules responsible for writing, reading, and erasing these modifications, known as epigenetic marks. These molecules are catalytic enzymes like histone acetyltransferases (HAT) and histone deacetylases (HDAC) which add and remove acetyl group on specific lysine residue of a particular histone type.

Hepatocyte-driven liver regeneration is a multistep process. The whole process is divided into three phases: (1) Priming phase, wherein the quiescent hepatocytes are triggered by cytokines and mitogenic signals to enter into cell cycle, (2) Proliferation phase, where the growth factors initiate the competent hepatocytes progression through the cell cycle, and (3) The growth-inhibitory phase that helps in termination of the process when the growth and proliferation associated with the regeneration essentially turn off as the homeostasis is maintained. A number of factors have been found to be associated with priming of the hepatocytes in order to divide during process of regeneration. These include norepinephrine, TNF-α, IL-6, serotonin, complement proteins, estrogens, and insulin. However, growth
Abstract

Factors like HGF, EGF, and TGF-α are involved in the cellular division. The dividing hepatocytes produce mitogenic signals which help other hepatic cells to divide.

The present study entitled as “Studies on epigenetic changes in liver regeneration during drug-induced liver injury in a murine model” involves the establishment of a liver injury model induced by thioacetamide using various biochemical, physiological, histological and immunological parameters. The regeneration process after liver damage was studied by analysing expression profile of specific genes semi-quantitatively and quantitatively, related to regeneration, growth and maintenance, stress, regulation of cell cycle and differentiation. Further, the role of histone modifications as active and repressive marks of transcription as well as markers of mitosis were explored at the level of tissue homogenate and at specific cells on liver tissue sections. These modifications showed a characteristic pattern of activation and suppression of transcription of the above mentioned genes during different stages from peak of injury till recovery/regeneration. Finally, modification status at promoter level was studied by chromatin immunoprecipitation for particular genes implicated to play an important role in liver regeneration.