The liver has tremendous potential to regenerate completely from the sustained injury. The survival of organisms suffering from liver damage completely depends on the regenerative capacity of the remaining hepatocytes. Usually death occurs when regenerative capacity of liver is compromised owing to heavy damage. During any mechanical or chemical injury, regeneration of liver is marked by the entry of quiescent cells into cell cycle. This division restores the liver mass and function under the process of compensatory hyperplasia. The increased metabolic stress on hepatocytes leads to rapid hepatocyte proliferation during regeneration. To complete the entire regeneration process, a vast majority of genes contribute at different stages of liver regeneration and are tightly regulated by epigenetic mechanisms.

At present, liver associated diseases have become a matter of concern. There are numerous factors that contribute to the diseased conditions such as hepatotoxic drugs like acetaminophen, CCl₄, thioacetamide, alcohol consumption, and disease-causing pathogens such as hepatitis virus, protozoan etc. These factors cause acute to chronic liver damage leading to cell death, cellular necrosis, inflammation, fibrosis, and cirrhosis of liver. To understand the underlying mechanism of liver damage and regeneration process, various disease models have been developed in the recent years. Hepatic injury models simulate various pathophysiological situations that are important in developing and evaluating improved pharmacological therapeutics. Investigations have revealed a similar regeneration response in case of drug-induced models of liver regeneration with greater clinical relevance.

There are different mechanisms proposed to be involved in the regeneration of liver. First, the hepatocyte-driven regeneration pathway, comprising a phenomenon of compensatory hyperplasia accomplished by the division of existing hepatocytes. Second, the liver progenitor cell-driven regeneration pathway involving division and differentiation of intrahepatic liver progenitor cells into functional hepatocytes. There are several models available to study mechanism and key factors regulating regeneration of liver.

Regeneration of liver is the result of molecular interplay, which is regulated by several genes 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 chromatin level by various other post translational histone modifications, 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 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 residues of a particular histone type.

The chromatin domains of every cell lineage contain characteristic epigenetic marks having specific distribution patterns inside nucleus. These patterns of epigenetic marks specifically, post-translational histone modifications are critically important. Thus, process such as transcription of genes is regulated by epigenetic marks especially histone acetylation (H3acK9) and methylation (H3me³K4). Both of these histone modifications are markers of active transcription. Whereas H3me²K9, H3me³K9, and H3me³K27 histone modification marks are known for repression of chromatin. There are several reports suggesting role of these post-translational histone modifications in activation of genes associated with cell division, proliferation, and suppression of genes of specialized liver function during ongoing process of hepatic regeneration and growth. Thus, by looking into all the above stated changes their regulatory roles in regeneration mechanism has been hypothesized.

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 using PCR. These genes are related to regeneration, growth and maintainance, stress, regulation of cell cycle and differentiation. Further, the roles of histone modifications as active and repressive marks of transcription as well as markers of mitosis were explored using immunoblotting and immunostaining. Finally, modification status at promoter level was studied by the chromatin immunoprecipitation for particular genes implicated to play an important role in liver regeneration.