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Investigating the Role of Genetic Variants in Drug- Induced Liver Injury

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Abstract

During drug research and the prescription of several licensed medications, drug-induced liver damage (DILI) continues to be a significant clinical issue. Despite being uncommon, there are grave repercussions. Numerous genetic risk factors, including specific HLA alleles and a few non-HLA genes that are immune-related and metabolic, have been identified as a result of ongoing research on genetic risk factors for DILI, particularly genomewide association studies. There is evidence for polygenic susceptibility involving pathways such as oxidative and endoplasmic reticulum stress and mitochondrial function for DILI induced by multiple drugs, but some non-HLA associations, like N-acetyltransferase 2 in isoniazid DILI and interferon regulatory factor 6 in interferon-beta DILI, are likely to be drug-specific due to the role of the associated gene. Enhanced comprehension of genetic risk factors ought to facilitate a deeper comprehension of the fundamental mechanisms behind DILI and enhance techniques for identifying hepatotoxic medications at an early stage of development. Genetic findings for several prevalent causes of DILI have been verified by HLA allele-specific T cell proliferation and in silico drug binding prediction to specific HLA proteins. Nonetheless, research conducted on hepatocytes exposed to elevated drug concentrations indicates the possibility of damage that is independent of genotype. It appears likely that a combination of genetic risk factors and other factors influencing medication levels contribute to susceptibility to DILI. Although there has been advancement in identifying genetic risk factors for DILI, limited positive predictive values indicate that genotyping patients before prescribing potentially hepatotoxic medications is not now helpful.

Keywords: Drug Induced Liver Injury, HLA Alleles, Hepatotoxic Drugs.

1 INTRODUCTION

The liver has a remarkable capacity to fully repair after suffering an injury. The ability of the surviving hepatocytes to regenerate is essential for the survival of creatures with liver injury. Usually, when the liver's ability to regenerate itself is severely damaged, death results. The entrance of quiescent cells into the cell cycle indicates the regeneration of the liver following any mechanical or chemical harm. Through the process of compensatory hyperplasia, this division restores the mass and function of the liver. Hepatocytes undergo heightened metabolic stress during regeneration, which causes them to proliferate quickly. To complete the full regeneration process, a large majority of genes contribute at different phases of liver regeneration and are closely regulated by genetic mechanisms (Michalopoulos & Bhushan, 2021). Drug-induced liver injury (DILI) is a serious health issue that affects the pharmaceutical business, drug regulatory organisations, and medical professionals. More than half of

cases of acute liver failure are due to DILI, which also includes paracetamol overdose-related hepatotoxicity (39%) and idiosyncratic liver injury (around 13%) that is brought on by other medications. In figure 1 shows the Schematic Diagram of Key Events Involved in DILI.

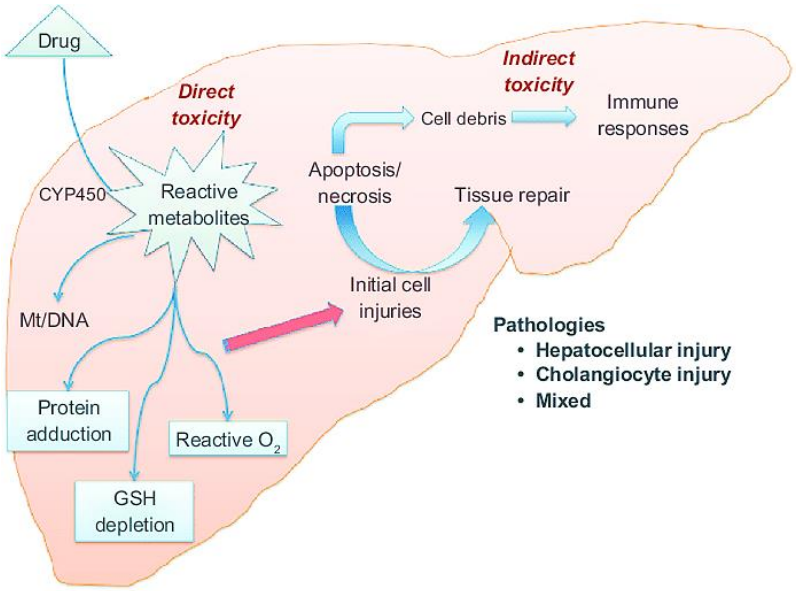

Figure 1: Schematic Diagram of Key Events Involved in DILI

The FDA in the United States has removed several medications off the market because to the high rate of morbidity and death linked to DILI. These consist of, among others, nefazodone, trovafloxacin, roglitazone, risperidone, and bromfenac. There are various ways that drug-induced liver damage manifests. These include drug allergy (immune system-induced production of antibodies against particular drugs), dosing-dependent toxicity (overdosage), and idiosyncratic toxicity (inherited specific genes that control the chemical transformation of that specific drug, causing accumulation of the drug or products of their metabolites that are harmful to the liver). While some medications directly harm the liver, others are converted by the liver into substances that can do the same. The symptoms and indicators of liver illnesses appear when medications damage the liver and interfere with its regular function.

The failure of the parenchyma cells to perform essential functions as a result of toxic or infectious agents, decreased mass of functioning cells, decreased blood supply, poor nutrition, and reactions of other organs to liver damage are the main causes of the metabolic disturbances that occur in liver diseases. A number of medications, their metabolites, and other substances are harmful to the liver cells and can cause a variety of ailments, including cholestasis, damage to specific liver cell structures or organelles, and even necrosis of the cells. Regeneration potential is restricted in cases of severe injury. Liver-related illnesses are a growing issue these days. Numerous factors, including alcohol intake, hepatotoxic medicines like acetaminophen, CCl4, and thioacetamide, and disease-causing microbes like the hepatitis virus and protozoa, among others, are linked to the sick states. These elements affect

the liver acutely or over time, resulting in fibrosis, inflammation, cellular necrosis, cell death, and cirrhosis (Björnsson, 2016).

Over the past 25 years, a thorough investigation of the genetics of DILI has been conducted utilising both candidate gene and genomewide association studies (GWAS). Even with the current state of knowledge, it is still not possible to use genetics to forecast a person's sensitivity to DILI or the likelihood that newly produced medications will be hepatotoxic. Despite these limitations, genetic research have generated useful data on underlying processes causing idiosyncratic DILI; studies integrating genetics and in vitro systems have advanced the field considerably (Daly, 2023). This work aims to examine the significance of genetic variants in DILI and explore how this understanding has influenced mechanism-based research. Prescription drug-related issues dominated early research on the genetics of DILI, but more recently, overlapping risk factors for the development of hepatotoxicity have been reported. There is now some information available regarding the genetic risk factors for DILI in relation to biologics; nevertheless, most research conducted thus far have focused on smaller molecules as the primary cause.

2 BACKGROUND

The liver is the most essential organ in mammals since it carries out all significant bodily processes that affect every system in the body. The liver is located in the abdominal cavity beneath the diaphragm and has a lobular shape. Compared to other organs, the liver's circulation system is unique. Venous blood from the small intestine, stomach, pancreas, and spleen makes up around 75% of the blood that enters the liver through the portal vein. All nutrients, medications, and other potentially hazardous chemicals are absorbed from this portal venous blood. The oxygenated blood that the hepatic artery transports from the pulmonary system to the liver makes up the remaining 25% of the arterial blood that the liver receives. The blood contents of the hepatic artery as well as hepatic portal vein empty into sinusoids. Sinusoidal blood flows towards each lobule's central vein, where it dumps its contents. The inferior vena cava receives deoxygenated blood from the liver via the hepatic veins (Vernon et al., 2018).

The connective tissue capsule known as Glisson's capsule envelops the liver, with the exception of the area where hepatic/bile ducts and blood arteries enter and exit the organ. Septae, or branches of connective tissue, are found all across the liver. The liver's connective tissue acts as a network, support system, and thoroughfare for bile ducts, lymphatic vessels, and afferent blood vessels. The liver's parenchyma splits into tiny sections known as lobules with the aid of a connective tissue sheet (Carotti et al., 2020).

The liver's structural component is made up of these hepatic lobules. Hepatocytes, a hexagon-shaped plate arrangement that emanates from a central vein, make up this lobule. The portal triad is a triangle made up of the portal vein, hepatic artery, and bile duct terminal branches. The thin-walled hepatic

sinusoids that exist in between the branching hepatic plates/cords and the lateral branches of these vessels confluence.

Because the endothelium of liver sinusoids lacks the basal membrane, they have a larger surface area than other capillaries for the exchange of metabolites between blood and hepatocytes. The endothelium and the hepatocyte plates are separated by the sub-endothelial gap known as the Disse or per sinusoidal space (Gracia-Sancho et al., 2021).

Hepatocytes, or liver parenchymal cells, make up 60–80% of all liver cells. Conversely, the remaining 20–40% of the liver cell population is made up of non-parenchymal cells like lymphocytes, kupffer cells, stellate cells, biliary epithelial cells, and sinusoidal endothelial cells (Fausto et al., 2012).

A significant portion of the hepatic cell population are hepatocytes. They are organised in single-cell cords or plates and have a polyhedral form. Tight junctions and intercellular adhesion complexes bind these hepatocytes together. Their other side, which is coated in microvilli, confronts the bile canaliculi, while their other side faces the persinusoidal area. Adult liver frequently contains binucleated cells with large polyploid nuclei. The majority of liver processes, including synthesis, detoxification, metabolism, and the storage of vitamins, carbohydrates, and fats, are carried out by hepatocytes. Along with other hepatic cells, they are also involved in secretory and excretory processes. distinct hepatocytes located in various hepatic lobule zones carry out these tasks. This zonation aids in the transportation of metabolites and has been linked to the direction of blood flow. Necrosis and damage are caused by the majority of hepatic toxins, and this differs depending on the lobule zonal distribution. Therefore, hepatocytes in the vicinity of the central vein are more vulnerable to damage than cells in the vicinity of the portal triad. In figure 2 Showing Cells of Liver and Blood Flow through Portal Vessels below.

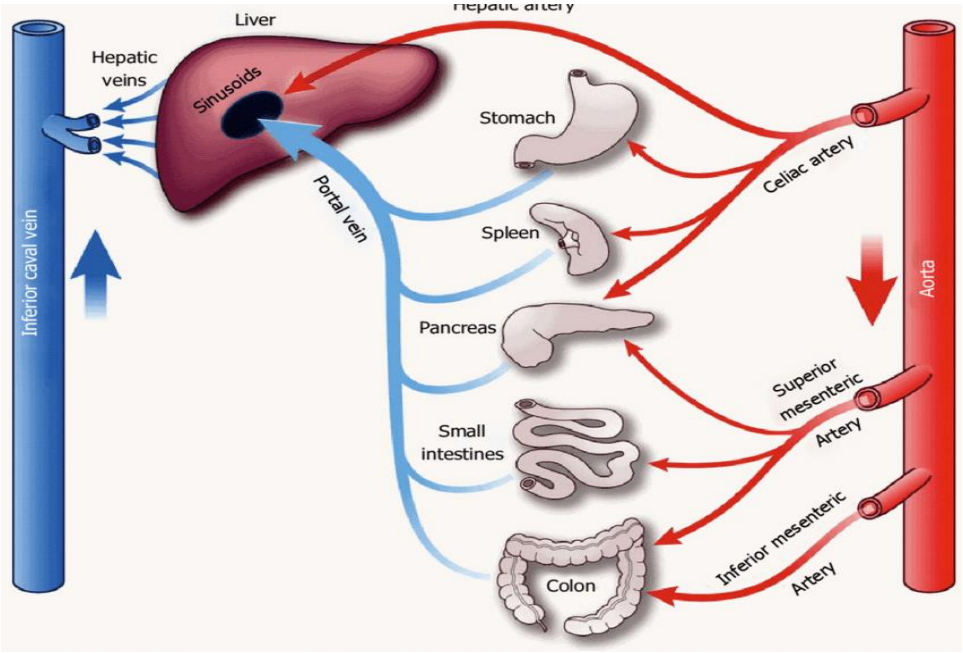

Figure 2: Showing Cells of Liver and Blood Flow through Portal Vessels

The most numerous resident macrophages in the liver are called kuffer cells. According to, they are affixed to the sinusoidal endothelium's luminal surface. These cells are necessary for the phagocytosis of invading organisms, foreign particles, and cytokine products (Dixon et al., 2013).

Within the Disse persinusoidal gap, in the nooks and crannies between the hepatocytes, are the hepatic stellate cells. These cells are linked to multiple processes, including cytokine secretion, vitamin A storage, and hepatic extracellular matrix formation. They become active during hepatic damage and are crucial to the development of fibrosis (Friedman, 2008).

Cholangiocytes, another name for biliary epithelial cells, are the cells that border the bile duct in portal triads (Banales et al., 2019). These biliary cells also line the canal of Hering, which connects the bile duct to the bile canaliculi, and the hepatocytes. They are engaged in modulating bile composition by adjusting solute and water content. Furthermore, it is now clear that leucocytes of the recipient graft are drawn to the biliary epithilium during liver transplantation.

The majority of the non-parenchymal cells in the liver are called endothelial cells. They line the intrahepatic circulatory arteries and offer a significant surface area for the absorption of nutrients. They provide a pathogenic and specific barrier when hepatocytes are exchanged from sinusoidal blood.

The parenchymal sinusoids of the liver are filled with lymphocytes. These lymphocytes are high in natural killer cells and NKT cells, which provide protection against invasive infections. They are also a component of the innate immune system.

In addition to its primary roles in nutrition distribution and storage, the liver serves as a cleansing organ. Chemicals that are absorbed through the gastrointestinal tract and consumed through food are absorbed by the liver. However, there is a risk that doing so will cause tissue damage due to the compounds that the liver breaks down and/or eliminates. The majority of these chemicals may either be used by the body in their intact form or further processed into parts of cells and tissues because they are compatible with cellular metabolic processing. However, chemicals that do not undergo additional processing or full metabolization enter the portal circulation and are subsequently processed by hepatocytes for excretion from the body. The unmetabolized compounds referred to as xenobiotics are broken down by enzymes, including those in the cytochrome P450 family. Free radicals are produced during this detoxification process, and reactive intermediates combine with proteins and DNA to form adducts that can harm or kill hepatocytes.

3 GENETIC VARIANTS DISEASES IN LIVER

During the detoxification process, the liver is exposed to a number of chemicals, including acetaminophenon, carbon tetrachloride, thioacetamide, and other chemical carcinogens. The amount of harmful substances determines whether the liver sustains an acute or chronic injury. Hepatocytes, the primary functional cell of the liver, are frequently damaged by them, and in chronic cases, death results (Bigoniya et al., 2009).

The liver is prone to several disorders since it is the primary organ involved in detoxification and metabolism. The length of time that pathological symptoms persist determines how severe an illness is. Diseases can be divided into acute and chronic categories based on this. Hepatic steatosis, jaundice, hepatitis, fibrosis, cirrhosis, cholestasis, and cancer (hepatocellular carcinoma and cholangiocarcinoma) are among the conditions that define them. Some common pathological conditions are described below:

Hepatic steatosis: Triglycerides deposited in hepatic cells rise abnormally in hepatic steatosis, a condition that results in fatty liver disease. Through regular fatty acid intake, synthesis, and esterification processes, the hepatocytes keep the body's triglyceride content constant. In addition to several metabolic, dietary, and hereditary factors, excessive alcohol consumption (AFLD) or obesity-related reasons account for the majority of the body's high triglyceride levels (NAFLD). Steatohepatitis is a severe form of fatty liver or steatosis accompanied by inflammation (Idilman et al., 2016).

Jaundice: Overproduction of bile pigment on liver cells is the hallmark of jaundice, which is sometimes referred to as hyperbilirubinemia. Disturbances in the liver cells' bilirubin absorption, transport, conjugation, and biliary excretion pathways could also be the cause. It may be brought on by harm, infection, or damage to the liver cells. On the other hand, jaundice may result from cholestasis (intra- or extra-hepatic) and lack of biliary excretion.

Cirrhosis A more severe form of liver fibrosis is called cirrhosis. It is associated with hepatic vasculature distortion. Widespread hepatic fibrosis with nodule formation is referred to as cirrhosis. Hepatic artery distortion results, as does blood supply impairment, scarring in the distal region, and loss of endothelial fenestrations. Cirrhosis is frequently characterised by decreased hepatocyte function as well as extensive proliferation and division. Alcohol misuse, hepatitis B and C, and autoimmune hepatitis are among the chronic liver illnesses that can lead to cirrhosis. It was also brought on by ongoing exposure to certain medications and poisons that cause hepatocyte necrosis and apoptosis.

A reasonable amount of death and morbidity is brought on by drug-induced hepatotoxicity. However, the lack of knowledge about the mechanism underlying medication-induced liver injury makes it a significant worry in the drug development process. The regeneration phenomena that occurs in mice after drug-induced liver injury has been the subject of multiple gene expression investigations employing microarray technology over the past ten years (Pandit et al., 2012). The priming stage of regeneration is when the majority of the changes in gene expression profiles take place. It facilitates the division of expression patterns into genes expressed immediately after birth and those expressed later.

A specific drug dosage caused acute liver failure, but repeated dosages can cause persistent harm such liver cirrhosis.

Different Drugs Used in Liver Cirrhosis

It is important to remember that different medications might affect liver tissue in different ways due to differences in their metabolic processes and regenerative mechanisms. In these kind of toxic models the processes of liver injury and repair are overlapping and/or tightly connected. The following discusses the effects of various frequently used compounds on liver damage and injury. These substances cause centrilobular liver damage by mechanisms of action that are comparable. More distal hepatocytes receive less oxygen and nutrients and are more vulnerable to ischaemic or nutritional damage, whereas hepatocytes closer to the portal triads receive oxygenated blood and nutrients and are therefore less vulnerable to harm. These substances' mode of action is dependent on the hepatic cytochrome P-450 system's bioactivation. As a result, the hepatocytes encircling the central vein are the primary targets for the harm caused by these substances.

Carbon Tetrachloride (CCl4), Using the cytochrome P-450 enzyme, a traditional hepatotoxicant breaks down the liver's metabolic byproduct to cause damage to the liver. Because it causes lipid peroxidation, the extremely reactive metabolite of CCl4 called trichloromethyl harms hepatocytes. Free radicals activate kupffer cells, which then release cytokines to aid in the healing process. During fibrosis, a single oral, intraperitoneal, or subcutaneous dose of CCl4 can cause an acute, reversible liver injury (Unsal et al., 2021).

Thioacetamide (TA), Depending on the amount and duration, a traditional hepatotoxicant is frequently employed to cause either acute or chronic liver damage. In most cases, thioacetamide causes centrilobular necrosis. Cytochrome P2E1 bioactivates thioacetamide to produce TA sulfoxide and TA-S,S-dioxide, which are harmful to liver tissue (Hajovsky et al., 2012).

D-galactosamine causes an intracellular uridine metabolite deficit, which results in hepatotoxicity. It is also linked to additional factors like endotoxinaemia. It is the cause of liver damage and fulminant liver failure. When compared to CCl4-induced liver regeneration, D-galactosamine-induced liver regeneration is less robust.

Acetaminophen is the most often used medication to cause acute liver failure by inducing liver poisoning. Acetaminophen often goes through glucuronidation and sulphation in the liver during its biotransformation process. The kidneys are used by the body to expel them. An excess of acetaminophen may impede its breakdown route therefore cytochrome P-450 oxidase system aids in acetaminophen metabolism.

Ethanol harms hepatocytes and is a hepatotoxicant. It is mostly linked to necrosis and steatosis of the liver. Variations in results are caused by different modalities of administration. Progenitor cells may become activated and the LPS-driven pathway may become involved with prolonged exposure.

The association of DNA wrapped around protein (histones) in a human diploid cell, measuring about two meters, is known as the chromatin. As a result, it keeps the vast majority of eukaryotic DNA inside

nuclear boundaries that have a diameter of around 10μm. Walther Flemming originally used the term "chromatin" in 1880 to describe a stainable substance found in nuclei used to analyse mitotic events with aniline dyes. The chromatin organisation is extremely dynamic and has hierarchical layers of complexity. Chromatin or DNA-protein interaction provides such a level of compaction.

DNA becomes inaccessible to the cell's enzymatic machinery due to the hierarchical level of compaction between chromosomal proteins and DNA. This affects DNA-dependent cellular processes including transcription and replication. The dynamic nature of chromatin modifies the temporal and spatial inhibitory effect of compact chromatin on cellular activities such as transcription and replication. The cell contains a variety of protein complexes and enzyme machinery that aid in the unwinding of chromatin, making DNA accessible for a variety of biological processes. Thus, there are two different states of chromatin that can exist, depending on what the needs of the cell are: (1) a compacted heterochromatic state, and (2) an open euchromatic state. While euchromatin has an even/lighter staining pattern, heterochromatin has differential/darker staining properties. While euchromatinized DNA is accessible to transcriptional machinery and transcriptionally active, heterochromatinized DNA is transcriptionally inactive (Allshire & Madhani, 2018).

4 RESEARCH OPPORTUNITIES AND RECOMMENDATIONS

The genetics of DILI is now well understood, primarily thanks to GWAS, but there is still much to learn about the underlying mechanism and genetic foundation. A growing number of patients are undergoing routine genome sequencing or using genotyping panels, which means that some electronic medical records may contain genomic information related to DILI risk. In the future, this data may be utilised to guide prescription decisions, particularly when a different medication that is less likely to cause DILI in a particular patient is available. It might be possible to conduct more genomic research on DILI, and studies that include recruiting more patients are being conducted to make this possible. Although there has been significant advancement in comprehending the genetics of idiosyncratic DILI recently, further research is necessary before pre-prescription genotyping may be widely used to prevent DILI reactions.

Any type of liver damage caused by over-the-counter or prescription pharmaceuticals is referred to as the DILI. There are two types of hepatotoxicity associated with drugs: non-idiosyncratic (predictable) and idiosyncratic (unpredictable). Based on the irregularities of liver function tests, DILI can be further divided into acute, chronic, cholestatic, hepatic, or mixed categories. Due to the direct toxicity of the medicine being delivered, the mechanism causing DILI may be metabolic or immune-mediated. A survey of the literature revealed that there are about 20 new cases of DILI for every 10,000 people annually. Since there are no particular biomarkers or histologic characteristics that point to a medicine as the source of liver injury, diagnosing DILI is challenging. There have been recommendations to employ specific DILI markers, such as microRNA 122, as biomarkers in high-risk

individuals. Although the study of genetic variants in DILI has a lot of potential, there are a number of obstacles and restrictions that make it more difficult to apply research results in clinical settings.

5 CONCLUSION

Genetic screening may provide a valuable tool for predicting the risk of DILI and tailoring medication therapy. However, additional investigation is required to completely understand the genetic pathways behind DILI and to create more thorough predictive models due to its complicated character, which is influenced by a variety of genetic and environmental factors. Personalised therapy can benefit from genetic variants' significant insights into the causes of DILI, but there are still a number of obstacles to overcome. Because DILI is a rare disorder, its aetiology is complex, and large-scale, carefully planned research are required to increase the statistical power of genetic discoveries. Furthermore, functional validation, a deeper comprehension of gene-environment interactions, and methods to get through practical and ethical obstacles are needed to translate genetic findings into clinical practice. In the future, resolving these issues will be essential to developing the industry and enhancing medication safety.

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