LIVER, ROLE OF NF-kB IN LIVER LINKING INJURY AND OTHER DISEASE

Deepak Phogat , Dept. of Pharmacy, Research Scholar, SunRise University, Alwar(Rajasthan)
Dr. Jagadish Chandra Pati , Associate Professor (Dept. of Pharmacy), SunRise University, Alwar (Rajasthan)

ABSTRACT

The liver is a vital organ responsible for numerous physiological functions, including metabolism, detoxification, and immune regulation. Hepatic injury, characterized by inflammation and hepatocyte damage, can lead to the development of various liver diseases, such as hepatitis, fibrosis, and cirrhosis. Nuclear factor kappa B (NF-κB) is a transcription factor that plays a crucial role in regulating the inflammatory response and immune system activation. This research paper aims to explore the involvement of NF-κB in liver injury and its connection to other diseases.

Keywords: NF-κB , Hepatocyte Damage , Detoxification, Inflammatory Response

INTRODUCTION

Overview of the Liver's Role in Metabolism, Detoxification, and Immune Regulation

The liver is a vital organ located in the upper right portion of the abdomen. It performs numerous essential functions that are crucial for maintaining overall health and well-being. Three key roles of the liver include metabolism, detoxification, and immune regulation.

Metabolism:

The liver plays a central role in various metabolic processes, including carbohydrate, lipid, and protein metabolism.

a) **Carbohydrate metabolism:** The liver helps regulate blood glucose levels by storing excess glucose as glycogen through a process called glycogenesis. When blood sugar levels drop, it breaks down glycogen into glucose through glycogenolysis and releases it into the bloodstream to maintain energy levels. The liver also converts excess glucose into triglycerides for storage.

b) **Lipid metabolism:** The liver synthesizes lipoproteins, such as cholesterol and triglycerides, and helps transport them to other tissues. It also metabolizes fatty acids, both from dietary sources and adipose tissue, for energy production and storage. Additionally, the liver produces bile, a substance that aids in the digestion and absorption of fats.

c) **Protein metabolism:** The liver plays a crucial role in protein metabolism. It synthesizes various plasma proteins, including albumin, clotting factors, and transport proteins. These proteins help maintain osmotic balance, contribute to blood clotting, and transport hormones, vitamins, and nutrients throughout the body. The liver also helps in the breakdown of amino acids, the building blocks of proteins, and eliminates toxic ammonia by converting it into urea, which is excreted in urine.

Detoxification:

The liver is responsible for detoxifying harmful substances, including drugs, alcohol, metabolic by-products, and environmental toxins. It utilizes two main processes for detoxification:

a) Phase I detoxification: In this process, enzymes in the liver, primarily cytochrome P450 enzymes, modify toxic substances to make them more water-soluble. This prepares them for elimination in the subsequent phase.

b) Phase II detoxification: In this phase, conjugation reactions occur, where water-soluble molecules produced in Phase I are further modified by attaching specific molecules, such as glutathione, sulfate, or glycine, to enhance their elimination from the body. The liver also helps remove bilirubin, a breakdown product of red blood cells, by conjugating it with glucuronic acid to form a water-soluble compound that can be excreted in bile.

Immune Regulation:

The liver has a significant role in immune regulation and surveillance. It contains a large population of immune cells, including macrophages called Kupffer cells. These cells help detect and eliminate pathogens, toxins, and cellular debris present in the bloodstream.

The liver also produces acute-phase proteins, such as C-reactive protein, fibrinogen, and complement proteins, in response to inflammation or infection. These proteins play important roles

in immune defense and tissue repair.Additionally, the liver is involved in immune tolerance, ensuring that the immune system does not overreact to harmless substances. It helps modulate immune responses to maintain a balance between protective immunity and tolerance to self-antigens or harmless environmental antigens.

Importance of Maintaining liver Homeostasis and the Consequences of Liver Injury

Metabolic Regulation: The liver plays a central role in regulating carbohydrate, lipid, and protein metabolism. Disruption of liver homeostasis can lead to metabolic disorders such as insulin resistance, dyslipidemia, and metabolic syndrome. This can contribute to the development of conditions like diabetes, obesity, and cardiovascular disease.

Detoxification: The liver is responsible for detoxifying harmful substances that enter the body, including drugs, alcohol, environmental toxins, and metabolic by-products. Liver injury can impair detoxification processes, leading to the accumulation of toxins, which can cause tissue damage and increase the risk of systemic toxicity.

Bile Production and Digestion: The liver produces bile, which aids in the digestion and absorption of fats. Liver injury can impair bile production and flow, leading to impaired fat digestion and malabsorption of fat-soluble vitamins. This can result in deficiencies of essential nutrients and disruption of normal digestive processes.

Protein Synthesis: The liver synthesizes various important proteins, including albumin, clotting factors, and transport proteins. Liver injury can lead to reduced production of these proteins, resulting in hypoalbuminemia, impaired blood clotting, and compromised transportation of hormones, vitamins, and nutrients.

Immune function: The liver plays a crucial role in immune regulation and surveillance. Liver injury can disrupt immune function, making individuals more susceptible to infections and impairing the body's ability to defend against pathogens.

Bile Excretion and waste Elimination: The liver excretes bilirubin, a waste product of red blood cell breakdown, into bile for elimination from the body. Liver injury can impair bilirubin excretion, leading to jaundice and the accumulation of bilirubin in the bloodstream.

Vitamin Storage and Activation: The liver stores and activates fat-soluble vitamins such as vitamin A, D, E, and K. Liver injury can affect the storage and activation of these vitamins, leading to deficiencies and associated health problems.

Hormone Metabolism: The liver metabolizes and eliminates various hormones from the body. Liver injury can disrupt hormone metabolism, leading to hormonal imbalances that can affect various physiological processes and contribute to hormonal disorders.

NF-κB Signaling Pathway

The NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling pathway is a crucial regulatory system involved in the control of various cellular processes, including immune responses, inflammation, cell survival, and differentiation. It plays a central role in both innate and adaptive immune responses. The NF-κB pathway is primarily composed of a family of transcription factors known as NF-κB, which consists of five members: RelA (p65), RelB, c-Rel, p50 (NF-κB1), and p52 (NF-κB2). These transcription factors are sequestered in an inactive state in the cytoplasm through binding to inhibitory proteins called IκBs (inhibitor of κB proteins). The activation of the NF-κB pathway can be initiated by various extracellular stimuli, including pro-inflammatory cytokines (e.g., tumor necrosis factor-alpha, TNF-α), pathogen-associated molecular patterns (PAMPs), such as bacterial lipopolysaccharides (LPS), and damage-associated molecular patterns (DAMPs), which are released during tissue damage or stress.

The canonical NF-κB pathway activation involves the activation of a receptor, such as the TNF receptor (TNFR), Toll-like receptors (TLRs), or interleukin-1 receptor (IL-1R), leading to the recruitment of adaptor proteins, such as MyD88 (myeloid differentiation primary response 88), TRAF (TNF receptor-associated factor), and IRAK (IL-1 receptor-associated kinase). This triggers a cascade of signaling events, eventually resulting in the activation of the IκB kinase (IKK)

complex. The activated IKK complex phosphorylates the inhibitory IκB proteins, targeting them for ubiquitination and subsequent degradation by the proteasome. This degradation releases NF-κB dimers from the cytoplasmic complex and allows them to translocate into the nucleus.

Structure and function of NF-κB transcription factors

Structure:

Rel Homology Domain (RHD): The RHD is a conserved DNA-binding domain found in all members of the NF-κB family. It consists of approximately 300 amino acids and is responsible for dimerization, DNA binding, and nuclear localization. The RHD contains characteristic structural motifs, including a dimerization domain (DD) and a DNA-binding domain (DBD). The DD facilitates dimer formation between different NF-κB family members, while the DBD allows specific binding to κB DNA sequences.

Transactivation Domains: NF-κB transcription factors contain transactivation domains (TADs) that are responsible for activating target gene expression. These domains interact with coactivators and the basal transcription machinery to initiate transcription. The TADs are located at the C-terminal region of the NF-κB proteins and exhibit variable sequences and lengths.

Nuclear Localization Signals (NLS): NF-κB proteins contain NLS sequences that facilitate their transport from the cytoplasm to the nucleus. The NLS signals allow the translocation of NF-κB dimers into the nucleus, where they bind to DNA and regulate gene expression.

Function: The NF-κB transcription factors act as key regulators of gene expression in response to various extracellular signals. Upon activation, NF-κB dimers translocate from the cytoplasm into the nucleus, where they bind to specific DNA sequences known as κB sites. This binding leads to the activation or repression of target gene transcription, depending on the context and the presence of coactivators or corepressors. NF-κB regulates the expression of genes involved in immune and inflammatory responses, such as cytokines (e.g., TNF-α, IL-6, IL-1β), chemokines, adhesion molecules, and enzymes involved in immune cell activation. These target genes are essential for orchestrating immune responses, coordinating cell survival, and modulating the inflammatory process. The activity of NF-κB is tightly regulated to prevent aberrant or prolonged activation. In the cytoplasm, NF-κB dimers are sequestered in an inactive state through binding to inhibitory proteins called IκBs (inhibitor of κB proteins). Upon activation, the IκBs are phosphorylated, leading to their degradation and the subsequent release and nuclear translocation of NF-κB dimers.

Activation Mechanisms of NF-κB, including Canonical and Non-Canonical Pathways

NF-κB (nuclear factor kappa B) is a transcription factor that plays a crucial role in regulating immune responses, inflammation, cell survival, and many other biological processes. The activation of NF-κB can occur through two main pathways: the canonical pathway and the non-canonical pathway.

Canonical Pathway:

The canonical NF-κB pathway is the most well-studied and is primarily involved in the regulation of acute immune responses and inflammation. It is triggered by a wide range of stimuli, including pro-inflammatory cytokines (such as tumor necrosis factor-alpha, TNF-α), interleukin-1 (IL-1), and microbial products (such as lipopolysaccharide, LPS).

The Canonical Pathway involves the following Steps:

a. Ligand binding: Upon stimulation, specific receptors on the cell surface recognize the external stimulus. For example, TNF receptor (TNFR) or IL-1 receptor (IL-1R) binds to their respective ligands.

b. Receptor Activation: Ligand binding induces a conformational change in the receptor, leading to the recruitment of adaptor proteins such as TNF receptor-associated death domain (TRADD) and receptor-interacting protein 1 (RIP1).

c. Formation of Signaling Complex: The recruited adaptor proteins facilitate the assembly of a multiprotein signaling complex called the TNF receptor-associated complex I (TNF-RI). This

complex includes proteins like TRAF2 (TNF receptor-associated factor 2) and IκB kinase (IKK) regulatory subunits.

d. Activation of IKK: The recruitment of IKK to the TNF-RI complex leads to the activation of IKK. The activated IKK complex consists of two catalytic subunits (IKKα and IKKβ) and a regulatory subunit (IKKγ or NEMO). IKK phosphorylates the inhibitory protein IκBα (inhibitor of κBα) at specific serine residues.

e. IκBα degradation: Phosphorylation of IκBα marks it for polyubiquitination, resulting in its degradation by the proteasome. This step liberates the NF-κB dimer from its inhibitory complex with IκBα.

f. Nuclear translocation: The liberated NF-κB dimer, typically composed of p50 and p65 subunits, translocates into the nucleus, where it binds to specific DNA sequences called κB sites and activates the transcription of target genes.

Non-canonical pathway:

The non-canonical NF-κB pathway is primarily involved in the regulation of lymphoid organ development, B-cell maturation, and adaptive immune responses. It is triggered by a subset of TNF receptor superfamily members, including CD40, B-cell-activating factor receptor (BAFFR), and receptor activator of NF-κB (RANK).

The non-canonical pathway involves the following steps:

a. Ligand binding: Stimulation of specific receptors, such as CD40, BAFFR, or RANK, by their ligands initiates the non-canonical pathway.

b. Receptor activation: Ligand binding induces the recruitment of TNF receptor-associated factor 3 (TRAF3) and cellular inhibitor of apoptosis protein 1 (cIAP1) or cIAP2.

c. Activation of IKKα: TRAF3 recruits and activates an enzyme called IKKα homodimer. This leads to the phosphorylation and processing of a specific NF-κB precursor protein called p100.

Experimental Models of liver Injury and their Relevance to human liver diseases

Chemical-induced liver injury:

Carbon tetrachloride (CCl4) or acetaminophen (APAP) administration: These chemicals can induce acute liver injury and mimic certain aspects of drug-induced liver injury (DILI) observed in humans.

Alcohol-induced liver injury: Chronic administration of ethanol can replicate alcoholic liver disease (ALD) and its progression, including steatosis, inflammation, fibrosis, and cirrhosis.

Surgical models:

Partial hepatectomy: Surgical removal of a portion of the liver leads to liver regeneration, which is relevant to studying liver regeneration processes and the underlying mechanisms.

Ischemia-reperfusion injury: Temporary occlusion of blood supply to the liver followed by reperfusion mimics liver ischemia-reperfusion injury observed during liver transplantation, liver surgery, or shock states.

Viral-induced liver injury:

Hepatitis virus infection models: Animal models infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) can mimic viral hepatitis and study the pathogenesis, immune response, and antiviral therapies.

Genetic models: Transgenic and knockout mice: Manipulation of specific genes involved in liver diseases can lead to the development of models that mimic human liver diseases, such as non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma (HCC), and hereditary liver disorders.

Inducible genetic models: These models allow the activation or inactivation of specific genes in the liver at a desired time point, providing insights into gene functions and their contributions to liver disease progression.

Cholestatic liver injury models:Bile duct ligation: Surgical ligation of the bile duct causes cholestasis, leading to hepatocyte injury, inflammation, and fibrosis, which are relevant to

cholestatic liver diseases like primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC).

Crosstalk between NF-κB and other Signaling Pathways Implicated in liver damage

Toll-like receptor (TLR) Signaling Pathway: TLRs recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), triggering immune responses. Activation of TLR signaling can induce NF-κB activation, leading to the production of pro-inflammatory cytokines and exacerbation of liver inflammation.

JNK (c-Jun N-terminal kinase) Signaling Pathway: JNK signaling plays a role in liver inflammation and hepatocyte apoptosis. NF-κB and JNK pathways can interact, with NF-κB promoting JNK activation and JNK enhancing NF-κB activity. This crosstalk contributes to hepatocyte death, inflammation, and liver injury.

MAPK (mitogen-activated protein kinase) Signaling Pathways: MAPK pathways, including ERK (extracellular signal-regulated kinase), p38, and JNK, are involved in liver damage and inflammation. NF-κB can be activated by MAPK signaling, and reciprocally, activated NF-κB can modulate MAPK pathway activation. This crosstalk regulates inflammatory responses, apoptosis, and tissue damage in the liver.

PI3K (phosphoinositide 3-kinase)/Akt Signaling Pathway: The PI3K/Akt pathway promotes cell survival and suppresses apoptosis. NF-κB activation can be regulated by Akt, and Akt-mediated NF-κB activation contributes to cell survival and resistance to apoptosis. In liver diseases, dysregulation of this crosstalk can influence hepatocyte survival and liver injury.

Wnt/β-catenin Signaling Pathway: Wnt/β-catenin signaling is critical for liver development and regeneration but dysregulation can lead to liver diseases, including hepatocellular carcinoma (HCC). NF-κB can interact with the Wnt/β-catenin pathway, with NF-κB activation inhibiting β-catenin signaling. This crosstalk affects liver regeneration and HCC progression.

Liver Cirrhosis: NF-κB-driven fibrogenesis and the development of hepatocellular carcinoma

NF-κB-driven Fibrogenesis:

Activation of Hepatic Stellate Cells (HSCs):

HSCs are the main contributors to liver fibrosis. In response to liver injury, NF-κB signaling is activated in HSCs, promoting their activation and transformation into myofibroblast-like cells, which are responsible for excessive production and deposition of extracellular matrix proteins, such as collagen.

Pro-inflammatory Cytokines:

NF-κB regulates the expression of various pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which are involved in the activation of HSCs and promotion of fibrogenesis. These cytokines contribute to the recruitment of immune cells, amplifying the inflammatory response and fibrotic processes.

Fibrogenic Mediators:

NF-κB signaling induces the production of fibrogenic mediators, including transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), and connective tissue growth factor (CTGF). These mediators stimulate HSC activation, collagen synthesis, and deposition, thereby promoting liver fibrosis.

NF-κB-driven Development of Hepatocellular Carcinoma (HCC):

Inflammation and DNA Damage:

Chronic inflammation associated with liver cirrhosis triggers DNA damage and genomic instability, predisposing hepatocytes to malignant transformation. NF-κB activation in the context of chronic inflammation contributes to the production of reactive oxygen species (ROS), DNA damage, and the activation of DNA repair mechanisms.

Survival and Proliferation Signals:

NF-κB promotes cell survival and proliferation through the upregulation of anti-apoptotic proteins (e.g., Bcl-2, Bcl-xL) and cell cycle regulators (e.g., cyclin D1). These signaling events driven by

NF-κB enhance the survival and expansion of transformed hepatocytes, favoring the development of HCC.

Immune Evasion and Metastasis:

NF-κB activation can facilitate immune evasion by modulating the expression of immune checkpoint molecules (e.g., PD-L1) and immunosuppressive cytokines. Moreover, NF-κB-mediated signaling pathways contribute to the acquisition of invasive and metastatic properties by HCC cells.

Current strategies for modulating NF-κB activity in liver pathologies

Pharmacological Inhibitors:

Small molecule inhibitors targeting specific components of the NF-κB pathway have been developed. These inhibitors can directly block the activity of NF-κB or upstream signaling molecules involved in its activation. Examples include IKK inhibitors (such as BAY 11-7082 and BMS-345541), proteasome inhibitors (such as bortezomib), and histone deacetylase inhibitors (such as suberoylanilide hydroxamic acid). These inhibitors have shown potential in preclinical studies and are being evaluated in clinical trials for liver diseases.

Natural Compounds:

Various natural compounds derived from plants have been shown to modulate NF-κB activity in liver diseases. For example, curcumin, resveratrol, and silymarin exhibit anti-inflammatory and antioxidant properties and can inhibit NF-κB activation. These compounds have demonstrated hepatoprotective effects in preclinical models and hold promise as complementary therapeutic options.

Targeting Inflammatory Cytokines and Chemokines:

In liver diseases associated with inflammation, targeting specific inflammatory cytokines and chemokines regulated by NF-κB can be effective. Monoclonal antibodies or small molecule inhibitors directed against pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and chemokine receptors have shown promise in clinical trials for conditions like non-alcoholic steatohepatitis (NASH) and autoimmune liver diseases.

MicroRNAs:

MicroRNAs (miRNAs) are small non-coding RNA molecules that regulate gene expression. Some miRNAs have been identified as regulators of NF-κB signaling in liver diseases. Modulating the expression of these miRNAs holds therapeutic potential. For instance, miR-122, which negatively regulates NF-κB activity, has been investigated as a therapeutic target in viral hepatitis and hepatocellular carcinoma (HCC).

Modulation of gut-liver axis:

The gut-liver axis plays a crucial role in liver diseases, and NF-κB signaling is implicated in this process. Strategies targeting gut dysbiosis and intestinal barrier function can indirectly modulate NF-κB activity in the liver. Probiotics, prebiotics, and selective antibiotics have been explored to restore gut microbial balance, enhance intestinal barrier function, and subsequently reduce liver inflammation mediated by NF-κB.

Challenges and Future directions in developing NF-κB-targeted therapies

Specificity of targeting:

NF-κB is involved in diverse cellular processes, including inflammation, immune responses, cell survival, and proliferation. Designing therapies that selectively target NF-κB signaling in specific cell types or disease contexts while sparing normal physiological functions remains a challenge. Future research should focus on developing strategies to enhance the specificity of NF-κB inhibitors to minimize off-target effects.

Complex NF-κB Signaling Network:

NF-κB signaling is a complex network with multiple components and cross-talk with other signaling pathways. Understanding the intricate regulatory mechanisms and feedback loops within the NF-κB pathway is crucial for developing effective targeted therapies. Future studies should

explore the crosstalk between NF-κB and other signaling pathways to identify potential synergistic or combinatorial therapeutic approaches.

Context-dependent Effects:

NF-κB can have opposing effects depending on the cell type, disease stage, and microenvironment. It can promote inflammation and cell survival in some contexts, while suppressing tumor growth or inducing apoptosis in others. Future research should focus on unraveling the context-dependent effects of NF-κB activation to optimize therapeutic strategies and identify patient subgroups that may benefit from NF-κB-targeted therapies.

CONCLUSION

By elucidating the involvement of NF-κB in liver injury and its connections to other diseases, this research paper provides insights into the pathogenesis of liver pathologies. Understanding the intricate mechanisms underlying NF-κB activation in liver diseases can pave the way for the development of targeted therapeutic strategies, potentially offering new avenues for the treatment of patients with liver injury and related disorders. In conclusion, NF-κB (nuclear factor kappa B) signaling pathway plays a critical role in linking liver injury and the development of various liver diseases. NF-κB activation is implicated in liver inflammation, fibrogenesis, hepatocyte apoptosis, and the progression of hepatocellular carcinoma (HCC).

In liver injury, such as chemical-induced liver injury or viral hepatitis, NF-κB is activated in response to pro-inflammatory cytokines, pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs). NF-κB activation leads to the production of pro-inflammatory cytokines, chemokines, and adhesion molecules, promoting immune cell infiltration and perpetuating the inflammatory response. Additionally, NF-κB-driven inflammation contributes to hepatocyte apoptosis and liver cell damage. NF-κB also plays a pivotal role in liver fibrogenesis, the hallmark of liver cirrhosis. Activation of hepatic stellate cells (HSCs) by NF-κB leads to their transformation into myofibroblast-like cells, which produce excessive extracellular matrix components, resulting in fibrosis and tissue remodeling. NF-κB-driven production of pro-inflammatory cytokines and fibrogenic mediators further exacerbates the fibrotic process.

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