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Mini Review

Role of NF-κB Signaling Pathway and Oxidative Stress in Liver Inflammation

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Abstract

Excessive inflammation is considered as a critical factor in many human diseases including liver diseases, cancer, obesity, type II diabetes, cardiovascular diseases etc. Oxidative stress and free radical generation associated with inflammatory diseases play a key role in diseases progression and pathology. Nrf2 is a member of the cap-N-collar family and the key transcription factor that regulates antioxidant response element-mediated expression of detoxifying antioxidant enzymes. Increase in expression of Nrf2 positively regulates the key antioxidant enzyme status during inflammation. The inhibition of inflammation by Nrf2 is associated with inhibition of the NF-κB pathway and inhibition of pro inflammatory cytokine production. So NF-κB and Nrf2 signaling pathway has been considered as a potential target for pharmacological intervention.

Keywords: Nuclear factor erythroid 2–related factor 2; Toll-like receptors; Nuclear factor-κB; Reactive oxygen species

Introduction

The liver is the most important organ located below the diaphragm in the right upper quadrant of abdominal cavity which plays a pivotal role in regulating various physiological processes such as metabolism, secretion, storage and detoxification etc. The major diseases that affect liver include alcoholic- related liver diseases, non-alcoholic fatty liver disease, hepatitis, haemochromatosis and primary biliary cirrhosis. The reactive oxygen species (ROS) and reactive nitrogen species (RNS) are usually generated in liver via normal metabolic and detoxification process [1]. However, sustained and excessive ROS cause cellular damage and have been linked to a variety of liver diseases [2]. Oxidative stress constitutes the background of viral and alcoholic liver diseases and participates in the liver fibrogenic response. The pathogenesis of the damage involves distinct cell type of the liver i.e., hepatocytes and stellate, endothelial and Kupffer cells and contributes to ischemia/regeneration, necrosis and apoptosis. These changes result in altered gene expression and progressive liver damage [2-5]. Antioxidant enzymes such as superoxide dismutase (SOD), catalase and glutathione peroxidase and nonenzymatic compounds like tocopherol, vitamin E, beta-carotene, ascorbate and glutathione (GSH) plays a protective role against ROS and RNS [6-8]. The chronic disease progression reduces the level of these essential protective antioxidants in the body leading to oxidative damage and release of various cytokines through induction of different inflammatory pathways.

Nrf2 Signaling Pathway in Liver Inflammation

The nuclear factor erythroid 2–related factor 2 (Nrf2) is an emerging regulator of cellular resistance to oxidants which controls the basal and induced expression of an array of antioxidant response element–dependent genes to regulate the physiological and pathophysiological outcomes of oxidant exposure [9]. Under basal conditions, Nrf2 is sequestered in the cytoplasm by an act in binding repressor protein Keap1, which facilitates its ubiquitination. Either oxidative or covalent modification of thiols in cysteine residues of Keap1 or Nrf2 by protein kinases results in dissociation of Nrf2 from Keap1. This dissociation process leads to its migration and binding to the ARE in the promoter regions of genes encoding the antioxidant and phase 2 detoxifying enzymes [10,11]. A major mechanism in the cellular defense against oxidative or electrophilic stress is activation of the Nrf2-antioxidant response element signaling pathway. Nrf2 directly affects the homeostasis of ROS and RNS by regulating the antioxidant defense systems through several mechanisms. Nrf2 play an important role in induction of catabolism of superoxide and peroxides through SOD, Prx, GPx, regeneration of oxidized cofactors and proteins, where GSSG is reduced by GSR, Trxox by TrxR and Prx-SO2H by Srx. The Nrf2 signalling has a pivotal role in synthesis of reducing factors, i.e., GSH by GCLC, GCLM, NADPH by G6PDH and 6PGD. The expression of antioxidant protein Trx and inhibition of expression of Trx inhibitor TXNIP; the increase of redox transport, such as cystine/glutamate transport through xCT; metal-chelation by MT1, MT2, ferritin; and induction of stress response proteins, such as HO-1 are also controlled by Nrf2 antioxidant response element pathway. Nrf2 also regulates the expression of several oxidant signaling proteins to impact a number of programmed cellular functions. Some regulators, such as p62 and DJ-1, activate Nrf2 and/ are induced by oxidants through Nrf2, creating a positive feedback loop with Nrf2. Many of the antioxidant enzymes/proteins regulated by Nrf2 localize in specific compartments within the cell to regulate redox signaling in the local environment [9]. The drug development based on Nrf2 signalling activation promises a potent target in controlling chronic inflammatory conditions associated oxidative stress mediated liver inflammation.

NF-κB Signaling Pathway in Liver Inflammation

Toll-like receptors (TLRs) are key molecule of the early innate

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immune defence mechanisms by activating canonical and non-canonical pathways of inflammation. Signal transduction pathways activated by Toll-like receptors have continued to be a major focus of research for investigators interested in the initiation of innate immune responses and the induction of pro-inflammatory cytokines and type I interferon's during infection. The common signaling pathways used by all members of the TLR super family are being targeted, with drugs that block nuclear factor-kappa B. Because nuclear factor-κB (NF-κB) is a ubiquitously expressed proinflammatory transcription factor that regulates the expression of over 500 genes involved in cellular transformation, survival, proliferation, invasion, angiogenesis, metastasis, and inflammation. TLRs such as TLR4 and TLR2 that detect PAMPs for instance LPS and lipoproteins are located on the cell surface whereas TLRs such as TLR3, TLR7 and TLR9 that detect viral RNA and DNA are located in the endosome [12]. Engagement of LPS and activation of the CD14/TLR4 complex activates downstream signaling molecules such as IRAK1/4, TRAF6 leading to activation of MAP kinases cellular signaling pathways in alcoholic liver disease and NFκB in the liver [13]. Activation of TLR2 and TLR4 induces NFκB dependent expression of cytokines and chemokines [14]. The activation of NF-κB leads to the transcription of hundreds of genes with κB binding sites, most of which are involved in the regulation of inflammation, immune responses and cell survival [15]. NF-kB is a critical activator of innate immune responses which are initiated with in epithelial or stromal cells of the infected tissue, as well as resident immune cells such as mast cells, DCs or Kupffer cells in the liver. Activation of NF-kB with in such cells leads to expression of cytokines and chemokines that recruit additional effector cells such as neutrophils and other leukocytes, resulting in a characteristic inflammatory response [16]. NF-kB pathway provides a new target in drug development for preventing and attenuating inflammatory diseases associated with liver.

Conclusion

This mini review discussed the various therapeutic targets associated with liver inflammation. This review may help to reveal the importance of drug development based on therapeutic targets associated with NF-kB and Nrf2 signalling pathway. The upregulated Nrf2 expression helps to overcome the oxidative stress created by ROS and RNS during inflammation. The downregulated expression of NF-kB gene may help to reduce inflammatory conditions associated with liver diseases. The drug development based on specific targets help to control chronic diseases with minimum or no side effect. The specificity of drug towards specific target genes promotes the safe use of drugs.

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