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The Role of NF-κB in hepatocarcinogenesis; Promoter or Suppressor?

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Abstract

The IκB kinase (IKK) subunit NEMO/IKKγ is essential for activation of the transcription factor NF-κB, which regulates cellular responses to inflammation. The function of NEMO in the adult liver remains elusive. Here we show that ablation of NEMO in liver parenchymal cells caused the spontaneous development of hepatocellular carcinoma in mice. Tumor development was preceded by chronic liver disease resembling human nonalcoholic steatohepatitis (NASH). Antioxidant treatment and genetic ablation of FADD demonstrated that death receptor-mediated and oxidative stress-dependent death of NEMO-deficient hepatocytes triggered disease pathogenesis in this model. These results reveal that NEMO-mediated NF-κB activation in hepatocytes has an essential physiological function to prevent the spontaneous development of steatohepatitis and hepatocellular carcinoma, identifying NEMO as a tumor suppressor in the liver.

NF-κB is a master regulator of innate immunity, inflammation, cell survival, proliferation and anti-apoptotic action [1]. Without stimulation, NF-kB is in an inactive state bound to its inhibitor IκB in the cytoplasm. Various agonists, such as IL-1, TNF α and TLR ligands, activate NF-κB. In general, after the receptors are stimulated with the corresponding ligand, intracellular signals activate the IκB kinase (IKK) complex, which is composed of 2 catalytic subunits, IKK1 (also known as IKKα) and IKK2 (also known as IKKβ), and a regulatory subunit NEMO (also known as IKKγ). The activated IKK complex phosphorylates IκB, leading to its subsequent polyubiquination and degradation. The free NF-κB undergoes nuclear translocation, where it binds to and stimulates transcription of target genes.

Although the link between chronic inflammation and carcinogenesis has been shown for many years, the pathophysiological mechanism has been elusive [2]. In fact, NF-κB is activated in various chronic liver diseases, such as cholestasis, autoimmune liver diseases and hepatitis B and C, which are highly associated with hepatocellular carcinoma (HCC) [3]. Various studies have demonstrated the involvement of NF-κB in cancer initiation, promotion, progression and metastasis in vitro and in vivo. In vitro studies have suggested NF-κB is involved in cancer cell survival and proliferation. Previous in vivo studies have yielded conflicting conclusions. In some studies, NF-κB inhibition suppresses cancer promotion and development. On the other hand, the inhibition of NF-κB can promote caricinogenesis. These contradictory results may result from the differential effects of NF-κB activation between hepatocytes and liver non-parenchymal cells, including Kupffer cells. Different types of cancer inducers, genetic background, genetic manipulation, and diet might determine the cell types of NF-κB activation.

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A previous study by Maeda et al clearly demonstrated that the specific deletion of IKK2 in hepatocytes ($IKK2^{LPC-KO}$) promotes chemically DEN-induced liver cancer [4]. In this mouse model, hepatocyte apoptopsis and compensatory hepatocyte proliferation were increased and associated with enhanced ROS production and JNK activity. In addition, the authors later also demonstrated that the sustained JNK activity in $IKK2^{LPCKO}$ mice plays a pivotal role for carcinogeneisis by using JNK1/IKK2 double KO mice [5]. Furthermore, the authors provide evidence that deletion of IKK2 in both hepatocytes and Kupffer cells suppress DEN-induced hepatocarcinogenesis, indicating that IKK2-deficency in Kupffer cells can suppress the enhanced liver cancer caused by the loss of IKK2 in hepatocytes. A key conclusion was that NF-κB activity in Kupffer cells contributes to cancer promotion and that NF-κB activity in hepatocytes acts as a cancer suppressor.

The most recent publication by Luedde et al reported that the specific loss of NEMO in hepatocytes ($NEMO^{LPC-KO}$) spontaneously induces chronic inflammation, steatohepatitis and liver cancer [6]. In $NEMO^{LPC-KO}$ mice, NF-κB activity in the liver was completely abolished, but not in $IKK2^{LPC-KO}$ mice, indicating that NEMO is essential for NF-κB activation, but there might be some residual NF-| B activity in IKK2 deficiency. This context might lead to the different phenotypes between the spontaneous carcinogenesis in $NEMO^{LPC-KO}$ mice and the carcinogenesis required chemical assault in $IKK2^{LPC-KO}$. Thus, the combination of these two publications let us know the critical role of NF-κB in hepatocarcinogenesis.

Young $NEMO^{LPC-KO}$ mice already display inflammatory cell infiltration and lipid deposition in the liver. Middle age 9 month old $NEMO^{LPC-KO}$ mice displayed severe steatohepatitis. Old age 12-month old $NEMO^{LPC-KO}$ mice had liver cancer.

The current study also examines the mechanism by which hepatocyte NEMO deficiency causes liver cancer. $NEMO^{LPC-KO}$ mice developed spontaneously more hepatic cell death and compensatory hepatic regeneration. Interestingly, hepatic progenitor cells, such as oval cells were strongly activated in this compensatory regenerative response. $NEMO^{LPC-KO}$ livers had sustained JNK phosphorylation which was accompanied by increased cytokine production such as TNFα, IL-6 and RANTES by non-parenchymal cells including Kupffer cells.

This study established the role of oxidant stress in NEMO-deficient carcinogenesis. The antioxidant butylated hydroxyanisole (BHA) markedly reduced hepatic inflammation, hepatocyte apoptosis, liver damage and steatohepatitis in $NEMO^{LPC-KO}$ mice. The previous and current papers focused on the signaling of TNFα, a potent activator of NF-κB in hepatocytes, as inducing hepatocyte apoptosis and carcinomas [1,3]. The current study shows that hepatic cell damage mediated by the loss of NEMO induces more TNFα production from Kupffer cells. Therefore, they generated the double knockout mice for NEMO and FADD, an adaptor molecule for TNF receptor type I required for the activation of caspase-8 and subsequent caspase-3. In these mice, all of the findings in $NEMO^{LPC-KO}$ mice, such as hepatic cell death, damage, compensatory regeneration and fat accumulation were reversed, suggesting that inflammation and lipid deposition are secondary consequence of hepatic cell death by NEMO deficiency in hepatocytes.

We can make the following conclusions from these papers on NF-κB-mediated hepatocarcinogenesis; First, NEMO is indispensable for NF-κB activation in hepatocytes. IKK2 plays an important role, but IKK1 may compensate in part for IKK2 deficiency. This would explain the differences between the NEMO- and IKK2- hepatocyte-deficient mice. Indeed, spontaneous-induced colitis model in IKK1/IKK2 double KO mice displayed a similar phenotype as NEMO KO mice in the most recent publication by Nenci et al [7]. Second, steatohepatitis and the promotion of liver cancer is a consequence of inflammatory cytokine production, such as TNFα from Kupffer cells stimulated with the products of necrotic cells

from repeated hepatocyte cell damage. Finally, Maeda et al demonstrated the critical concept about the different roles of NF-κB in hepatocytes and Kupffer cells. The loss of NF-κB activity in hepatocyte promotes hepatocarcinogenesis. In contrast, NF-κB deficiency in Kupffer cells or the NF-κB deficiency in both hepatocytes and Kupffer cells suppresses tumor generation.

Thus, the inhibition of NF-κB might be a therapeutical strategy for liver cancer, because the loss of NF-κB in Kupffer cells might suppress cancer even with its potential promotion by the loss of NF-κB in hepatocytes. However, we must be careful to understand anti-NF-κB therapy for cancer, because drugs may preferentially act on specific cell types. We must keep in mind that a drug that preferentially suppresses hepatocyte NF-κB may enhance liver cancer. Does this concept suggest that the pharmacologically inhibition of NF-κB activity predominantly in Kupffer cells could become a therapy for hepatocellular carcinoma? Selective inhibition of NF-κB in Kupffer cells also may suppress innate immune responses, leading to immunocompromised hosts. Thus, these publications provide new insights into the molecular mechanism of the contribution of NF-κB to carcinogenesis, but we still require further study into whether the control of NF-κB activity is sufficient for cancer therapy without severe side effects.

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