Canonical NF-κB signaling in hepatocytes acts as a tumor-suppressor in hepatitis B virus surface antigen-driven hepatocellular carcinoma by controlling the unfolded protein response.

Chronic hepatitis B virus (HBV) infection remains the most common risk factor for hepatocellular carcinoma (HCC). Efficient suppression of HBV viremia and necroinflammation as a result of nucleos(t)ide analogue treatment is able to reduce HCC incidence; nevertheless, hepatocarcinogenesis can occur in the absence of active hepatitis, correlating with high HBV surface antigen (HBsAg) levels. Nuclear factor κB (NF-κB) is a central player in chronic inflammation and HCC development. However, in the absence of severe chronic inflammation, the role of NF-κB signaling in HCC development remains elusive. As a model of hepatocarcinogenesis driven by accumulation of HBV envelope polypeptides, HBsAg transgenic mice, which show no HBV-specific immune response, were crossed to animals with hepatocyte-specific inhibition of canonical NF-κB signaling. We detected prolonged, severe
endoplasmic reticulum stress already at 20 weeks of age in NF-κB-deficient hepatocytes of HBsAg-expressing mice. The unfolded protein response regulator binding immunoglobulin protein/78-kDa glucose-regulated protein was down-regulated, activating transcription factor 6, and eIF2α were activated with subsequent overexpression of CCAAT/enhancer binding protein homologous protein. Notably, immune cell infiltrates and liver transaminases were unchanged. However, as a result of this increased cellular stress, insufficient hepatocyte proliferation due to G1/S-phase cell cycle arrest with overexpression of p27 and emergence of ductular reactions was detected. This culminated in increased DNA damage already at 20 weeks of age and finally led to 100% HCC incidence due to NF-κB inhibition. The role of canonical NF-κB signaling in HCC development depends on the mode of liver damage; in the case of HBsAg-driven hepatocarcinogenesis, NF-κB in hepatocytes acts as a critical tumor suppressor by augmenting the endoplasmic reticulum stress response. (Hepatology 2016; 63:1592-1607).