Ablation of IFNγ enhances hepatocarcinogenesis by promoting activation of STAT3 and JNK

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IFNγ suppresses diethylnitrosamine-induced liver injury and hepatocarcinogenesis

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IFNγ plays an important role in different types of cancers. Many studies have shown that IFNγ helps reject transplanted tumors by the mechanisms such as enhancing cytotoxicity to cancer cells and inhibiting angiogenesis. However, there is also evidence showing that IFNγ promotes cancers, such as colorectal carcinomas, by inducing chronic inflammation. In human hepatocarcinogenesis, the function of this cytokine is still under debate. Unexpectedly, we found that IFNγ-/- mice were more susceptible to the liver injury induced by diethylnitrosamine (DEN), a widely used chemical hepatocarcinogen. Furthermore, spontaneous liver injury and hepatocyte necrosis were observed in 10 months old IFNγ-/- mice and sparse liver carcinogenesis was observed in IFNγ-/- mice males over 15 months old. Therefore, we hypothesize that loss of IFNγ increases the susceptibility to liver cancer in mice. To test this hypothesis, we use IFNγ-/- mice to generate both spontaneous and chemical-induced liver cancer models to study initiation and development of liver cancer. FXR-/- mice spontaneously develop liver cancer when they are 15 months old regardless of genders. Deletion of IFNγ in FXR-/- mice led to early liver tumorigenesis when they were only 8 months old. In the DEN-induced liver cancer model, IFNγ-/- mice developed a much higher number of tumors with increased sizes than wild-type mice. Enhanced hepatocyte necrosis, compensatory proliferation, and inflammation were observed in IFNγ-/- mice in both models, which contribute to their enhanced liver tumorigenesis. STAT1 phosphorylation was reduced in aged and DEN-treated IFNγ-/- mouse livers, which was correlated to the increased STAT3 activation. Furthermore, we found that aging induced activation of NF-κB and p53 in wild-type mouse livers, but ablation of IFNγ greatly reduced this age-related activation, and promoted ROS production and activation of proto-oncogenes STAT3 and c-Jun. In conclusion, ablation of IFNγ leads to hyperactivation of STAT3 and JNK signaling after liver damage and promotes hepatocarcinogenesis. IFNγ is an essential tumor suppressor in liver1-10.

Further reading

References:


