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EDITORIAL

FoxM1 Induces CCl2 Secretion From Hepatocytes Triggering Hepatic Inflammation, Injury, Fibrosis, and Liver Cancer

Hepatocellular carcinoma (HCC) is the most frequent primary malignancy of the liver and constitutes the third leading cause of cancer death worldwide.[1] Virtually all HCCs arise in patients with chronic liver disease such as chronic viral hepatitis, nonalcoholic fatty liver disease, and alcoholic liver disease. Although etiologic agents such as hepatitis B virus or alcohol are known carcinogens, the reasons for hepatocellular transformation are not fully understood for the majority of chronic liver diseases. Currently, it is believed that chronic injury and the ensuing compensatory hepatocyte proliferation, inflammation, and fibrosis promote the development, survival, and outgrowth of mutated hepatocyte clones that ultimately form HCCs. Among these, hepatocyte proliferation and inflammation may contribute to hepatocellular transformation via reactive oxygen species and replication-induced mutagenesis, respectively.

The study by Kurahashi et al[2] investigates the FoxM1, a transcription factor with important functions in proliferation and oncogenesis, suggesting novel functions for FoxM1 in the context of HCC development. FoxM1 is known to play a key role in cell cycle progression, chromosomal segregation, and genomic stability by increasing the expression of a wide range of G2/M-specific genes such as cyclins A, B1 and B2, Cenpf, Plk1, Nek2, Aurkb, Birc5, Plk1, and Cdc25B and down-regulating the expression of CDK inhibitors p21 and p27.[3] Accordingly, FoxM1 is highly expressed during S and G2/M phases and predominantly found in highly proliferative tissues as well as the majority of cancers including HCC.[4] Previous studies using hepatocyte-specific deletion of FoxM1 revealed its key role in driving tumor-promoting proliferation in mouse models of HCC.[5] Moreover, studies in human HCC and mice also demonstrated a role for FoxM1 in genomic stability of HCC.[6] Kurahashi et al now demonstrate that hepatocyte-specific overexpression of FoxM1 leads to spontaneous liver injury, inflammation, fibrosis, and HCC. The authors show that up-regulation of the chemokine CCl2 within the hepatocyte compartment represents an early event in FoxM1-driven liver injury. CCl2 from FoxM1-overexpressing hepatocytes triggers macrophage recruitment and the subsequent development of liver injury, fibrosis, and most likely also HCC. Accordingly, the authors found a FoxM1-binding site in the promoter of murine CCl2. Moreover, they demonstrated reductions of liver injury, inflammation, and fibrogenic gene expression in FoxM1 transgenic mice after hepatocyte-specific GalNAC-siRNA-mediated CCl2 silencing. Likewise, depletion of macrophages by liposomal clodronate reduced markers of liver injury such as serum alanine aminotransferase and hepatic deoxyuridine-5'-triphosphate biotin nick end labeling staining. Finally, inhibition of FoxM1 by thiostrepton reduced serum alanine aminotransferase, hepatic deoxyuridine-5'-triphosphate biotin nick end labeling staining, CCl2 expression, and F4/80-positive hepatic macrophages in a high fat–high cholesterol model of nonalcoholic steatohepatitis as well as in FoxM1-transgenic mice. Of note, the authors did not observe a significant reduction of Ki67+ proliferating hepatocytes in mice treated with thiostrepton. Together, these findings suggest that FoxM1 may contribute to liver inflammation and injury and most likely also hepatocarcinogenesis through CCl2-dependent and proliferation-independent pathways. Similar findings had already been shown in the lung, where epithelial overexpression of an active form of FoxM1 promoted inflammation (including CCl2 up-regulation) but not proliferation.[7]

Although the study by Kurahashi et al[2] has used carefully designed approaches and hepatocyte-specific tools such as GalNAC-mediated CCl2 silencing to characterize the role of FoxM1 in hepatic injury, some questions remain unanswered. Most importantly, the study does not fully answer how FoxM1 triggers hepatocyte death. The authors proposed that FoxM1-induced CCl2 triggers hepatocyte death, and that this is dependent on Kupffer cells. However, the authors did not show that hepatocyte expression of CCl2 is sufficient to induce cell death, fibrosis, and HCC. Moreover, macrophage depletion by liposomal clodronate did not fully abrogate cell death. It is conceivable that FoxM1 overexpression triggers events besides CCl2 induction in hepatocytes. As such, high levels of FoxM1 without up-regulation of other parts of the cell proliferation machinery could drive hepatocytes into mitotic catastrophe or promote genomic instability as previously suggested.[6] Both could contribute to inflammation, injury, and cancer development in addition to CCl2. Moreover, the mechanism by which CCl2 and recruited macrophages kill hepatocytes needs to be further investigated because these cells typically efferocytose dead cells rather than being actively involved in cell death induction.[8] Finally, it would be important to confirm the effects of thiostrepton with a second FoxM1 inhibitor because thiostrepton might inhibit additional pathways.

Together with previous studies on FoxM1 in HCC,[4,5] results from this study suggest that treating HCC with FoxM1 inhibitors such as thiostrepton may have therapeutic benefits. Although there have been vast improvements in HCC with increasing success of immunotherapy and novel combination therapies, all successful medical HCC therapies target the tumor microenvironment. Drugs that target FoxM1 might be a first case in which direct targeting of tumor cells has beneficial effects. However, it remains to be determined whether this leads to side effects in non-tumor liver tissue in advanced cirrhosis, and whether targeting FoxM1 affects fast-proliferating extrahepatic tissues such as the intestine.

In conclusion, further understanding of FoxM1 in HCC is needed before it can be considered as target for preclinical and clinical studies.

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