Perspective

Can we stop the progression of chronic liver disease to hepatocellular carcinoma?

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Comment on: Qin G, Luo M, Chen J, *et al*. Reciprocal activation between MMP-8 and TGF-β1 stimulates EMT and malignant progression of hepatocellular carcinoma. Cancer Lett 2016;374:85-95.

Abstract: Transforming growth factor beta 1 (TGFβ1) and matrix metalloproteinase 8 (MMP-8) appear to play important roles in the pathogenesis of hepatocellular carcinoma (HCC). TGFβ1 is pro-fibrogenic while MMP-8 promotes metastasis by degrading collagens in the extracellular matrix. However, both of these molecules have tumor suppressing as well as tumor promoting properties. The study by Qin *et al*. examines the relationship between TGFβ1 and MMP-8 in tumor progression, and suggests that they operate reciprocally in a positive feedback loop. While this is an important observation that would ultimately benefit tumor bearing patients, there is also additional evidence that the consequences of altered TGFβ1 signaling and elevated MMP-8 expression impact the pathogenesis of chronic liver disease (CLD) long before the appearance of HCC. This raises the possibility that these molecules could be targeted and regulated early enough to delay or prevent the development of cirrhosis and/or HCC.

Keywords: Hepatocellular carcinoma (HCC); transforming growth factor beta 1 (TGFβ1); chronic liver disease (CLD)

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Hepatocellular carcinoma (HCC) is the fifth most frequent cancer in the world and now the second leading cause of cancer related deaths (1). There are many treatments for people diagnosed with this tumor type, and part of the reason for this has to do with the heterogeneity of HCC at the cell and molecular levels. This idea may be the reason why a single therapeutic approach is successful in only a modest proportion of diagnosed patients (1). Thus, there has been great interest in identifying and in therapeutically targeting, molecular steps in the pathogenesis of HCC. The paper by Qin *et al*. (2) adds to the growing literature that attempts to better define the role of matrix metalloproteinase 8 (MMP-8) and transforming growth factor beta 1 (TGFβ1) in tumor pathogenesis.

Most HCC is associated with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections (3). While these viruses are essentially non-cytopathic, they do trigger immune responses that often inflict considerable liver damage without clearing infected cells. The host response to these repeated bouts of chronic liver disease (CLD) involves regeneration of hepatocytes (a cellular response), but over time, there is also an increase in stellate cell activation (4), with corresponding increases in extracellular matrix production (an acellular response) that is referred to as fibrosis (i.e., scarring). When fibrotic bundles accumulate and connect up in three dimensions, variably sized islands of hepatocytes become encased in nodules of extracellular matrix referred to as cirrhosis. At the molecular level, TGFβ1 is known to be strongly pro-fibrogenic, and is likely to promote the pathogenesis of CLD (5). In addition, the paper by Qin *et al*. (2) shows that there is a reciprocal activation of TGFβ1 and MMP-8 in HCC cell lines. Given that MMP-8 is a protease that contributes to the degradation of extracellular matrix, its up-regulation in cirrhotic and HCC nodules may promote tumor progression and metastasis.

The paper by Qin *et al*. (2) points out that TGFβ1 promotes epithelial-mesenchymal transition (EMT) and malignant progression in HCC, which is consistent with the role of TGFβ1 in other tumor types (6). Importantly, TGFβ1 expression is activated in the livers of mice that were transgenic for the HBV oncoprotein, hepatitis B x (HBx), prior to the appearance of tumors (7). Independently, TGFβ1 was up-regulated in hepatoma cell lines expressing HBx (8). Further evidence has shown that HBx expressing hepatocytes stimulate the production of TGFβ1 via paracrine mechanisms that activate hepatic stellate cells (9). Activated hepatic stellate cells developed increased expression of collagen I, connective tissue growth factor (CTGF), alpha smooth muscle actin, matrix metalloproteinase-2, and TGF-β1, together with enhanced proliferation (9). Given that HBx is abundantly expressed in the liver of chronically infected HBV carriers with cirrhosis (10,11), suggests that up-regulated expression of TGFβ1 occurs prior to the appearance of tumors and is involved in much more than EMT that accompanies tumor progression. In this context, the architecture of the acini in normal liver is almost completely missing in cirrhotic liver nodules, implying that EMT may also occur intrahepatically long before the appearance of HCC. Interestingly, HepG2 (human hepatoblastoma) cells expressing HCV core protein also activated the expression of TGFβ1, TGFβ receptor II, alpha-smooth muscle actin and CTGF when co-cultured with primary hepatic stellate cells (12), suggesting that both HBV and HCV actively contribute to the development of fibrosis and cirrhosis that are known risk factors for HCC. In addition, significant increases of CTGF and TGFβ1 were observed in a stable HCV E2-expressing Huh7 cell line (13), although it is not known whether E2 mediates these changes *in vivo*. Additional observations also suggest a tight correlation between HCV infection and altered TGFβ1 signaling in patients with CLD that promotes the appearance of fibrosis and cirrhosis (14). In this case, TGFβ1 signaling activates c-Jun N-terminal kinase (JNK), which converts the mediator Smad3 into two distinctive phospho-isoforms, which in turn, mediate a switch from TGFβ1 negative growth regulation to stimulation of growth and fibrogenesis (14). Similarly, HBx shifts hepatocyte TGFβ1 signaling from the tumor-suppressive to the oncogenic pathway in the liver (15), suggesting that altered TGFβ signaling is an early event in fibrogenesis. With regard to signaling pathways that promote fibrosis, HCV E2 stimulates Janus kinase (JAK), ERK1/2 and p38 (13). Importantly, HBx also up-regulates JAK (16) and ERK1/2 (17), further suggesting a common denominator that contributes to fibrogenesis at the molecular level. The finding that HBx (18) and HCV (19) activate ras (20), which is upstream of ERK1/2, further supports this hypothesis, and underscores the idea that therapeutic intervention in a few shared signaling pathways may be effective in slowing or inhibiting CLD progression among patients infected with either or both of these viruses.

The paper by Qin *et al*. points out that MMP-8 and TGFβ1 form a positive feedback loop through activation of PI3K/Akt/Rac1 signaling (2). While the activation of this signaling pathway promotes hepatocellular survival, proliferation and migration, independent observations have also shown that both HBV (through HBx) (17,21) and HCV (through NS5A) (21,22) constitutively activate this pathway in the pathogenesis of HCC. Importantly, constitutive activation of PI3K/Akt signaling mediates changes in gene expression which trigger EMT (23). In fact, HCV was shown to trigger EMT in primary hepatocytes via activation of PI3K/β-catenin signaling (24). If this occurs in infected liver, it may represent type II EMT, which mediates wound healing as well as tissue reconstruction, regeneration and fibrosis (25). This is distinct from type III EMT, which involves the transformation of epithelial cells into mesenchymal cells during tumor metastasis (26), and is the context in which the Qin *et al*. study was performed (2). Both viruses also activate ras and ERK signaling (15,18,27,28), which promote proliferation. Independent studies have shown that both viruses activate NF-κB (29,30) and β-catenin (31-33). Thus, it is proposed that the activation of these combined pathways (PI3K/Akt, ras, NF-κB, β-catenin and TGFβ1) trigger type II EMT in the infected liver and type III EMT in the tumor. In the chronically infected liver, these viruses may promote cellular survival and proliferation in order for virus infected cells to persist, and continue replicating virus, in the presence of ongoing immune responses aimed at eliminating virus infected cells. Although this study was not done in the context of HBV or HCV infection, these same pathways are also activated (or remain activated) during tumor progression. Given that TGFβ1 promotes fibrogenesis and that MMP-8 (and other MMPs) degrades the extracellular matrix that encase cirrhotic nodules, it seems likely that the expression levels and activity of HBV and HCV proteins may regulate the extent to which MMP-8 and TGFβ1 are expressed. For HBV, this may reflect the extent to which integrated virus sequences exist and their ability to be transcribed and translated into HBx, while for

HCV, this may reflect the levels of HCV replication in the liver. Both HBV integration and levels of HCV replication would be influenced, in turn, by immune responses against virus infected cells. However, the fact that TGFβ promotes fibrogenesis while MMP-8 does the opposite (2) provides a dynamic model in which the extent of fibrosis may vary over time, and may help to explain how some patients have progressive CLD and die of end stage liver disease (cirrhosis) while the pathogenesis of CLD in others arrests or even reverses as in cases where the grade of fibrosis decreases or when cirrhosis becomes inactive. In this context, it can also be envisioned that the reciprocal activation between MMP-8 and TGFβ1 may also play a significant role in EMT and the migration of hepatocytes that appear to take place as the architecture of the liver undergoes major changes in the course of CLD.

The environment in which hepatocytes exist within cirrhotic nodules is in stark contrast to that which existed in the normal liver. For example, the intimate association between hepatocytes and the portal blood supply is destroyed by the accumulation of extracellular matrix that is characteristic of fibrosis and cirrhosis. The fact that hepatocytes become surrounded by connective tissue in a cirrhotic nodule, characterized by the scarce presence of portal triads (hepatic artery, hepatic vein, and bile duct) as well as central veins (connecting to the systemic circulation), means that the cells within such nodules have to survive in regions of local hypoxia. Under these circumstances, the cells that are best able to survive and proliferate are hepatic progenitor or stem-like cells (34). In this context, the finding that HBx up-regulates the expression of stem cell markers (35,36) suggests a mechanism whereby HBx expression in the liver contributes to hepatocarcinogenesis. HCV also activates signaling pathways that promote the development of cancer stem cells (CSC) (37,38) *in vitro* (39) and in mouse models of hepatocarcinogenesis (39-41). Given that it takes several decades after infection to develop HCC, the activation of TGFβ1 seems to be a common event in the pathogenesis of CLD leading to HCC.

One of the pathways that HBx constitutively activates *in vivo* that contributes importantly to the appearance of HCC is Hedgehog [Hh; (42)] which normally regulates tissue homeostasis, cellular proliferation and contributes to stem cell maintenance (43). Constitutive activation of Hh signaling up-regulates the expression of Kras, c-myc, TGFβ1 and β-catenin (44), which also activate the Hh signaling molecule and transcription factor, Gli (44). In early hepatocarcinogenesis, Gli may block apoptosis in DNA damaged, immortalized cells, thereby further promoting tumor development. Activated Kras, c-myc, TGFβ1 and β-catenin are associated with either EMT and/or "stemness", again suggesting early roles in carcinogenesis. Given that a fibrogenic response is common in both chronic HBV and HCV infections, one would also expect Hh activation in HCV infections. Elevated production of Hh ligands were observed in the liver of both HBV and HCV patients, and the presence, frequency and distribution of these ligands directly correlated with the extent of liver fibrosis (45). Hh signaling was also activated in human liver cancer cell cultures shortly after infection with HCV (46). In fact, it has been proposed that activated Hh signaling may be a prognostic marker for HCC (47), further implicating Hh signaling in the pro-fibrogenic response that accompanies the expansion of liver progenitor cells that eventually develop into cancer stem cells.

In the normal liver, TGFβ1 is a negative growth regulator, but in the context of carcinogenesis, TGFβ1 signaling is altered and TGFβ1 becomes a tumor promoter (48). These differences may result from mutational inactivation of the TGFβ1 signaling pathway. However, negative growth regulatory signaling may be blocked by non-canonical kinases that promote growth and survival, such as MAPK, which inactivates the TGFβ signaling molecules smad2/3 by phosphorylation (49). In this context, perhaps it is not coincidental that both HBV and HCV are tumor associated viruses that constitutively activate MAPK (50). MMP-8, which degrades collagen, also demonstrates dual functions, such as pro- and anti-inflammatory properties, as well as pro- and anti-tumor effects, depending upon the biological system used and the experimental design (51). For example, production of MMP-8 by neutrophils increases the access of inflammatory cells to sites of tissue damage. Chronic tissue damage is an important risk factor for promoting the development of many tumor types, including HCC. In contrast, MMP-8 has been shown to promote the differentiation of monocytes into M2 macrophages (52). Although M2 macrophages contribute to tumor associated inflammatory responses, these responses protect the tumor from immune elimination. If M2 macrophages are generated during CLD, they would block the elimination of infected hepatocytes in chronically infected patients, as well as the elimination of HCC cells in tumor bearing patients. Independent observations have shown that tumor associated macrophages promote cancer stem cell-like properties via TGFβ1-induced EMT (53). The fact that altered TGFβ1 signaling is also mildly immunosuppressive (48),

suggests that MMP-8 and TGFβ1 may work additively or synergistically in promoting chronic virus infection, and later on, in tumorigenesis. However, MMP-8 production may also contribute to wound healing by slowing down or preventing the progression of CLD to fibrosis and cirrhosis (54,55), thereby acting as a tumor suppressor (51,56). The study by Qin *et al* (2), suggests that TGFβ1 and MMP-8 promote tumor progression, although most of the data shown is from *in vitro* experiments, and the relevance of these observations to *in vivo* data remains to be elucidated in future work. Having said that, the Qin *et al*. study (2) brings attention to the roles that TGFβ and MMP-8 plays in the pathogenesis of HCC, although as discussed above, this may only be the tip of the iceberg.

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