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SHORT COMMENTARY

Insulin Resistance—a Link Between Inflammation and Hepatocarcinogenesis?

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Abstract: The incidence of hepatocellular carcinoma (HCC) is increasing world wide. The risk factors for the development of HCC include liver cirrhosis, chronic alcohol intake, and chronic viral hepatitis. These conditions are associated with inflammation, liver cell injury, and oxidative stress. The signaling pathways that contribute to liver cell injury have been shown to also promote insulin resistance in hepatocytes. On the other hand, obesity and diabetes have been suggested as risk factors for the development of chronic liver disease and HCC. The molecular mediators (e.g. stress kinases) and signaling pathways that contribute to cellular injury, proliferation and insulin resistance are also activated in chronic liver disease. At this time it is still unknown whether (1) IR will help to identify patients that are of increased risk for progressive liver disease or (2) if improving IR will be beneficial to patients with chronic liver disease. Future research will have to expand our knowledge on mediators of inflammation and liver cell injury within clinical trials to establish whether IR should be included in every hepatologists work up as a cofactor for chronic liver disease.

Keywords: insulin resistance, HCC, JNK, IKK, TNF, apoptosis

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The incidence of hepatocellular carcinoma (HCC) is increasing worldwide and the mortality rate of this cancer has doubled over the last two decades.[1] Liver cirrhosis is considered a major risk factor for the development of HCC, however in a subset of patients with chronic liver disease HCC develops in the absence of cirrhosis and the etiology of HCC remains occult in one third of all patients.[2,3] It has been proposed that these patients develop HCC from cryptogenic cirrhosis related to non-alcoholic fatty liver disease (NAFLD).[4,5] The disease spectrum of NAFLD ranges from fatty liver to non-alcoholic steatohepatitis (NASH) which can progress to fibrosis and end stage liver disease.[6] The risk factors associated with the development of NAFLD include visceral obesity and insulin resistance (IR) or frank diabetes. Epidemiological studies have found that these factors also contribute to the risk to develop HCC independent of the underlying liver disease.[7] Despite the strong epidemiological evidence supporting a mechanistic involvement of IR in hepatocarcinogenesis and chronic liver disease, the underlying mechanisms are only incompletely understood.

The factors that contribute to hepatic insulin resistance in chronic liver disease are (1) chronic inflammation and oxidative stress (ROS), (2) steatosis, and (3) pro-inflammatory cytokines and adipokines.[8,9] At a molecular level, it has been demonstrated that intracellular accumulation of lipids promotes oxidative stress in hepatocytes. Fatty acids and ROS lead to the activation of intracellular stress kinases that block insulin signaling pathways in hepatocytes directly through inhibitory phosphorylation of insulin receptor substrates (IRS) resulting in decreased activation of downstream effector molecules in response to insulin. Prominent among these is the c-Jun N-terminal kinase (JNK) that causes insulin resistance through increased serine phosphorylation of IRS molecules. Secondly, ROS activate residential macrophages in the liver (e.g. Kupffer cells) resulting in the release of proinflammatory cytokines.[10,11] Among these cytokines, tumor necrosis factor α (TNF) has been studied most extensively and is known for its ability to induce insulin resistance through activation of JNK and promote apoptosis and liver cell injury. Deletion of TNF, the TNF receptor or JNK was shown to prevent insulin resistance from obesity or steatohepatitis.[12–14] Additional scientific evidence to support the role of chronic inflammation in hepatocarcinogenesis comes from studies in mice that exhibit impaired activation of the transcription factor nuclear factor kappa B (NFκB). Hepatocyte-specific deletion of NEMO, a regulatory subunit of the IKK complex which regulates NFκB activation, abolishes NFκB transcription.[15] These mice exhibit chronic liver inflammation with increased cell death, steatohepatitis, and HCC. Based on these observations, it has been hypothesized that chronic inflammation promotes insulin resistance, liver injury and carcinogenesis even in the absence of liver cirrhosis. In support of this hypothesis, two recent clinical studies have found that improvement of liver disease in patients with chronic HCV infection prevents the onset of diabetes and that patients suffering from liver disease exhibit increased levels of pro-inflammatory cytokines which promote IR.[16,17]

The role of insulin or insulin analogues in carcinogenesis is highly debated since insulin and insulin-like growth factor (IGF) activate signaling pathways that stimulate cellular proliferation and cell survival.[18,19] Overexpression of the IGF-I receptor and high levels of IGF-I or II ligand promote proliferation and tumor cell growth, while IGF-II receptor which is known to antagonize proliferation is frequently deleted in HCC.[20] Among the signaling pathways that are activated in response to insulin, the phosphoinositol-3-kinase (PI3K)-Akt and the Ras-Raf-MEK-Erk pathway contribute to carcinogenesis.[21,22] Recently, the SHARP trial established the multikinase inhibitor sorafenib for the systemic treatment of advanced HCC and found that inhibition of tyrosine kinase signaling pathways improves survival in HCC.[23] Subsequent studies have aimed to inhibit insulin signaling in addition to the Ras-Raf-MEK-Erk pathway and synergistic effects in reducing the viability of HCC were observed ex vivo.[24]

In a recent issue of Clinical Medicine: Endocrinology and Diabetes Donadon and co-authors examined the prevalence of IR and the degree of β-cell dysfunction in patients with chronic liver disease.[25] Patients with chronic liver disease from (1) chronic HCV infection, (2) cirrhosis without HCC and (3) HCC were studied. The authors found that the degree of IR increased with the severity of liver disease as determined by the homeostasis model assessment of insulin resistance (HOMA-IR). Healthy controls

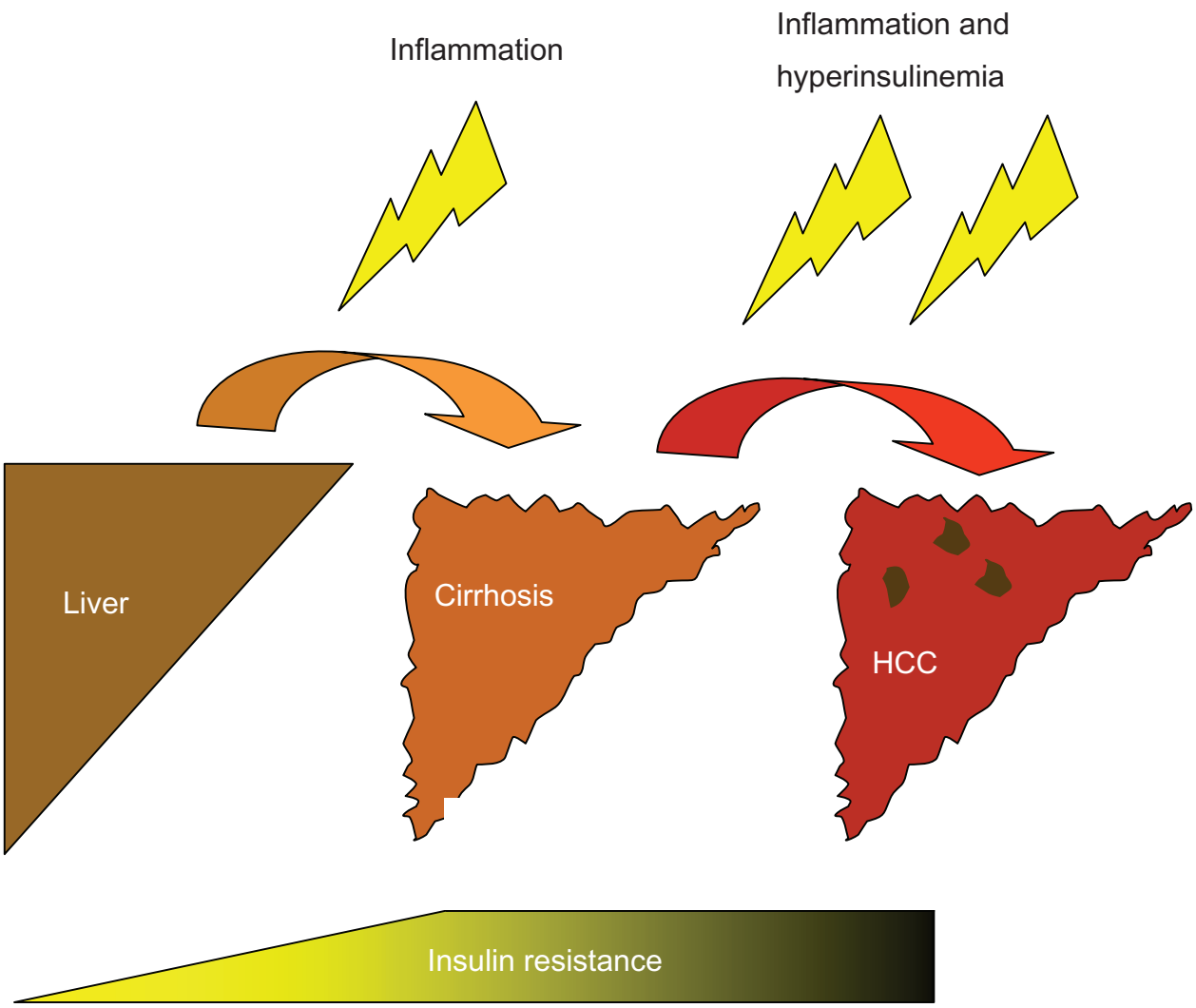

Figure 1. Schematic of the progression of chronic liver disease to HCC. Chronic liver disease involves low grade of inflammation and oxidative stress leading to decreased insulin sensitivity in hepatocytes. Hyperinsulinemia could be a "secondary hit" to propagate proliferation of pre-malignant cells in the cirrhotic liver promoting the development of HCC.

exhibited a physiological degree of insulin sensitivity, patients with chronic HCV infection had intermediate levels of IR, and patients with liver cirrhosis had the highest degree of IR. Interestingly, patients with HCC had HOMA scores comparable to patients with "only" cirrhosis. These results are in line with previous observations that insulin resistance occurs in patients with advanced liver disease, especially in chronic HCV infection and NAFLD and implies that IR proceeds cirrhosis and HCC.[26–28] In addition to IR, the authors examined β-cell function employing the HOMA-β index and observed high levels of insulin secretion and thus higher insulin resistance in patients with chronic HCV infection or HCC than in patients with cirrhosis. These findings give rise to speculations about the role the endocrine pancreas in the development of HCC: (1) does hyperinsulinemia promote HCC in chronic liver disease and (2) does a decrease in insulin levels, as observed in β-cell failure or improvement of IR delay HCC development in cirrhosis?

In summary, insulin resistance is a likely cofactor in chronic liver disease which is aggravated by inflammation associated with the underlying liver disease and which potentially contributes to hepatocarcinogenesis. Although HCC is a very heterogeneous disease with differences in the genetic and biological background, improving insulin sensitivity in patients with chronic liver disease could have a beneficial effect on the outcome of treatment. Prospective studies are

required to evaluate the effect of insulin sensitizers in chronic liver disease to potentially improve the clinical outcome or decrease the incidence of HCC.

Disclosure

The author reports no conflicts of interest.

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