Role of Iron in Hepatocellular Carcinoma

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Evidence of the Role of Iron Overload in Hepatocellular Carcinoma

A direct role of iron in hepatocarcinogenesis has been suggested on the basis of the evidence that patients with hereditary hemochromatosis (HH) had a 200-fold greater risk of developing hepatocellular carcinoma (HCC) than the general population.[1] The risk of HCC developing in HH patients is higher than that of patients with non–HH-related chronic liver diseases, matched for sex, age, and severity of liver fibrosis.[2] It has been shown in case-control studies that African subjects with dietary iron overload have a higher HCC risk as well.[3] Moreover, HCC has been described in several patients with transfusion-associated iron overload or iron overload related to ineffective erythropoiesis.[4]

Mechanisms of Iron Toxicity in HCC

One of the major, as yet unsolved dilemmas is whether iron exerts its oncogenic potential indirectly, through the induction of cirrhosis, or whether it also has direct carcinogenic activity. The possibility that free iron can exert an oncogenic potential is related to its ability, being electronically unstable, to induce oxidative stress. Reactive oxygen species production, in physiologic conditions controlled by antioxidant intracellular defense mechanisms, can lead to lipid peroxidation and oxidative damage to several cellular membranes and organelles, including DNA. Thus, excess free iron with reactive oxygen species overproduction in hepatic tissue, exceeding the cellular defenses, could be responsible for mutagenesis and hepatocarcinogenesis, overcoming the protective effect of activation of tumor suppressor genes and critical DNA repair genes orchestrated by p53[5-7] (Fig. 1). This implies that, even in the presence of minor degrees of hepatic iron excess, patients may be exposed to an increased risk of cancer. Experimental evidence also supports a role for iron in HCC development in animal models, even in the absence of cirrhosis,[8] thereby suggesting that iron has a direct effect on HCC. This is further supported by the observation that patients with noncirrhotic HH may develop HCC, albeit rarely.

Iron as a Cofactor in the Pathogenesis of HCC

It has also been suggested that iron plays a role in HCC development in chronic liver diseases associated with minor iron overload/siderosis. Among conditions associated with minor degrees of increased iron deposition, the more prevalent include chronic hepatitis C virus (HCV) hepatitis, alcoholic liver disease and nonalcoholic fatty liver disease (NAFLD) associated with insulin resistance and the metabolic syndrome (Table 1). The most widely held hypothesis is that oxidative stress can be induced by these different etiologies and that liver iron promotes injury and fibrosis acting synergistically with the initial etiologic insult.[9,10] Interestingly, it has been shown that HCV is able to interfere with iron metabolism, inhibiting hepatic transcription of hepcidin, the key iron metabolism regulatory hormone, which is in turn followed by increased liver iron deposition.[11] Less well-defined is the interaction of alcohol and NAFLD with hepcidin, with conflicting evidence supporting or refuting an inhibiting effect on hepcidin transcription (Fig. 2).

To address the possible wider role of iron in hepatocarcinogenesis, several authors have studied *HFE*, the gene responsible for most cases of HH, in diverse liver diseases. In patients with chronic liver disease and mild iron overload, conflicting results concerning a possible association between *HFE* status and HCC have been reported (Table 2).[12-15] In a prospective study of 301 consecutive patients with cirrhosis, it was found that liver iron overload and heterozygosity for the C282Y *HFE* mutation were associated with a higher risk of HCC in patients with alcoholic

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HH, hemochromatosis; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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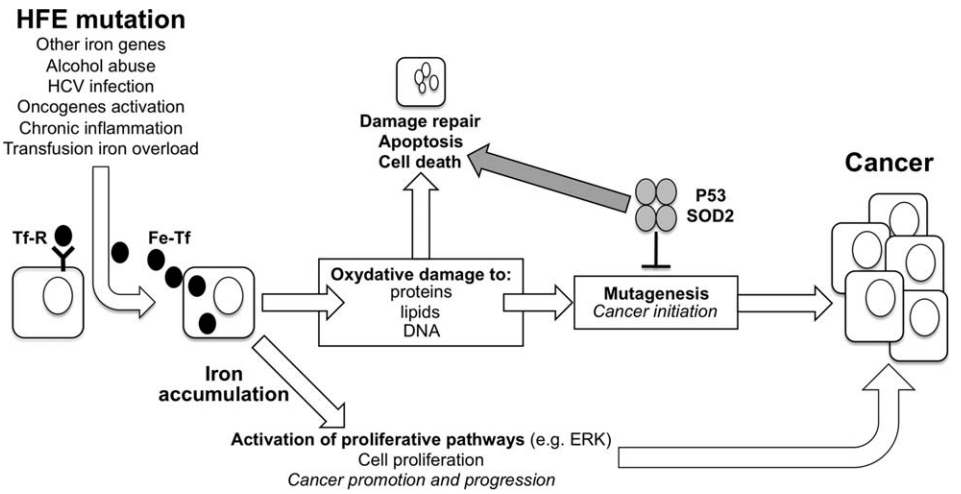

Figure 1 The hypothesized mechanisms of iron toxicity in hepatic carcinogenesis. The free iron induces oxidative stress with overproduction of reactive oxygen species, that, exceeding the physiological cellular defenses, can lead to lipid peroxidation and oxidative damage to several cellular membranes and organelles, including DNA.

TABLE 1 Role of Iron Overload as Co-Factors in Chronic Liver Disease

Chronic Liver Disease	Studies
Alcoholic liver disease	Experimental models, humans
Porphyria Cutanea Tarda	Humans
Non alcoholic Fatty Liver Disease (NAFLD)	Experimental models, humans
Chronic viral hepatitis	
HCV-related chronic hepatitis	Experimental models, humans
HBV/HDV liver disease	Humans
Hepatocellular Carcinoma	Experimental models, humans
End stage liver disease	Experimental models, humans
Portosystemic shunting	Experimental models, humans
Chronic liver disease in Diabetes	Experimental models, humans

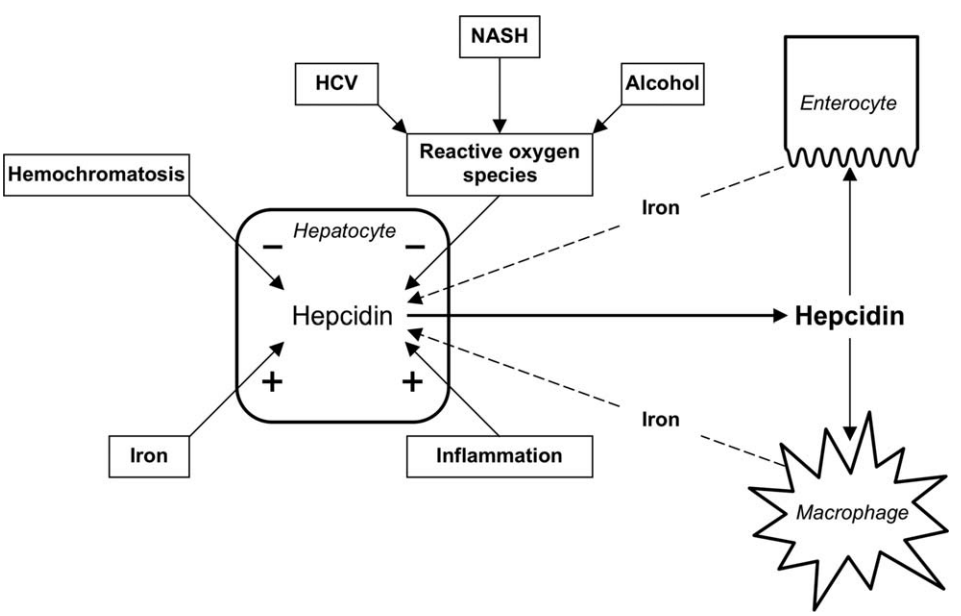

Figure 2 The role of iron in liver disease. Oxidative stress in the liver can be induced by HCV, alcohol, NASH, hemochromatosis, and inflammation. Oxidative stress can depress the expression of hepcidin, the key regulator of iron metabolism that controls duodenal iron absorption and iron release from macrophages.

TABLE 2 Studies on the Possible Association Between HFE Mutations and the Risk of HCC Development

Author	Reference	N Cases	Patients	Study Design	C282Y pos (%)	HFE/HCC Association
Pirisi M	Cancer, 2000	61	HCC	Case -control	11	No
Beckman LE	Oncology, 2000	54	HCC	Case-control	20	Yes
Lauret E	Am J Gastroenterol, 2002	77	HCC	Case-control	16	Yes in alcoholic cirrhosis
Hellerbrand C	Clin Gastroenterol Hepatol, 2003	137	HCC	Case-control	12.4	Yes
Boige V	Gut, 2003	133	HCC	Case-control	5	No
Cauza E	Am J Gastroenterol, 2003	162	HCC	Case-control	5	Yes in HH
Willis G	BMC Gastroenterology, 2005	144	HCC	Case-control	17	Yes in HH
Fracanzani AL	Blood Cell Mol Dis, 2005	303	HCC	Case-only	4	Association with HBV
Repero	Rev Esp Enferm Dig, 2007	196	HCC	Case-control	8	No
Nahon P	Gastroenterology, 2008	162	Alcoholic cirrhosis	Prospective	8	HR 2.7 (1.2-6.3)
		139	HCV-related cirrhosis		12	HR 0.2(0.5-1.2)
Ezzkiouri S	Arch Med Res, 2008	96	HCC	Case-control	1	No
Motawi TK	Gene, 2013	79	HCV cirrhosis	Prospective	0	No

Most of the references reported in Jin (14)

but not HCV-related cirrhosis.[16] In addition, it has been shown that patients with polymorphisms of oxidant/antioxidant enzymes were at increased risk of cancer.[17] Similarly, it has been reported that the risk of HCC is higher in patients who have nonalcoholic steatohepatitis (NASH)–related cirrhosis with hepatic iron excess.[18] However, the absence of a clear association in NAFLD between iron accumulation and *HFE* mutations means that there is no value in assessing risk of HCC in NASH-related cirrhosis by testing for *HFE* mutations.[19]

Iron Depletion as a Therapeutic Option

It is an open question whether iron depletion therapy, either by phlebotomy or iron chelation, may reduce the risk of HCC. In the only available prospective study, which included a small series of patients with HCV-related cirrhosis, patients who underwent phlebotomy had a reduced risk of HCC.[20] This study needs to be confirmed in a prospective longitudinal well-powered study. Interestingly, iron depletion by phlebotomy was associated with a reduced risk of developing cancer in a randomized trial including a large series of subjects with peripheral vascular disease.[21]

In conclusion, iron excess may be considered a potential oncogenic factor. Controlled clinical studies are needed to propose iron depletion as a HCC preventive therapy. ■

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