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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

HIF2α Activation in NASH: A New Force Pushing Toward HCC

Nonalcoholic fatty liver disease (NAFLD) is currently recognized as the most common cause of chronic liver disorder, with an alarming and growing global prevalence of 25%.[1] A significant proportion of patients with "simple steatosis" (20%–30%) may develop nonalcoholic steatohepatitis (NASH), in which triglyceride accumulation is accompanied by hepatocellular injury, inflammation, and fibrosis.[1] Importantly, NASH patients can progress to cirrhosis and end-stage liver disease, but they may also develop hepatocellular carcinoma (HCC), the most frequent liver cancer and an almost incurable tumor.[1,2] In fact, NAFLD/NASH is emerging as the most common risk factor for HCC.[2] It is noteworthy that NAFLD-related HCC is strongly associated with the degree of liver fibrosis but independent of cirrhosis, in contrast with other HCC etiologies such as hepatitis C virus infection.[2] In spite of active research in the field, there are still no effective therapies available for NASH,[3] and the efficacy of those currently used to treat HCC such as immune checkpoint inhibitors seems to be lower in NAFLD-HCC patients.[4,5] In view of all these considerations, the identification of mechanisms critical for NASH progression and NASH-associated HCC development[2,6] appears essential for the development of effective therapeutic strategies.

Hypoxia-inducible factors (HIFs) are a family of transcription factors activated by low O_2 availability. HIFs consist of a heterodimer of an O_2-sensitive α-subunit (HIF1α or HIF2α) and a constitutively expressed HIF1α subunit. Under normoxic conditions, HIFα proteins are rapidly hydroxylated by a group of O_2-dependent prolyl hydroxylase domain (PHD) enzymes and subsequently degraded by the proteasome. However, hypoxia limits the activity of PHD enzymes, leading to the stabilization and accumulation of HIFα proteins and the activation of their target genes' expression[7] (Figure 1). Importantly, the expression and activity of HIFα proteins can also be triggered by hypoxia-independent stimuli from the cellular microenvironment.[8] HIFα-target genes participate in multiple cellular functions from metabolic adaptation to O_2 and nutrient deprivation to angiogenesis, cell proliferation, adhesion, and migration. Therefore, HIFs have been traditionally involved in the pathogenesis of cancer.[8] More recently, evidence has emerged indicating that the HIF pathway has a central role in metabolism regulation and may influence metabolic diseases such as diabetes, obesity, and NAFLD.[9] Importantly, although HIF1α and HIF2α show structural similarity, both factors have different patterns of tissue expression, functional properties, and transcriptional targets.[10] In this context, activation of HIF2α, but not that of HIF1α, triggers liver inflammation, steatosis, and fibrosis.[9,11] Consistently, hepatocellular HIF2α deletion attenuates dietary-induced fibroinflammation and NAFLD progression.[12] Although all this evidence cogently supports a role for HIF2α in the pathologic evolution of NAFLD, the involvement of this factor in HCC development has remained controversial.[13–15] In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Parola and co-workers provide cogent experimental evidence of the contribution of HIF2α to NASH-related liver cancer.[16]

Consistent with a previous report,[15] Flogia et al[16] confirmed the up-regulation of HIF2α protein in a significant proportion of NAFLD-related HCC patients in association with poorer clinical outcomes. To directly test the involvement of HIF2α in NASH-HCC development, hepatocyte-specific HIF2α null mice (*hHIF2α*$^{-/-}$) received a single diethylnitrosamine injection and were subsequently fed a NASH-inducing choline-deficient L-amino acid-defined diet for 25 weeks. In agreement with human findings, HCCs arising in this NASH context in wild-type (*Wt*) mice also showed increased HIF2α expression. However, and most interestingly, the number and size of tumors developed in *hHIF2α*$^{-/-}$ animals were significantly reduced compared with *Wt* mice. These differences were accompanied by a less fibrotic and inflammatory tumoral microenvironment in HIF2α-deficient mice, and as could be expected, markers of cellular proliferation and cell cycle progression were enhanced in tumors from Wt animals. Mechanistically, besides the already known HIF2α-dependent activation of the protumorigenic cysteine-proteases inhibitor SerpinB3,[17] one remarkable finding of this study was the stimulatory effect exerted by HIF2α on YAP expression and the downstream up-regulation of c-Myc levels, which was demonstrated not only in cultured cells but also in tumors from Wt and *hHIF2α*$^{-/-}$ mice. This HIF2α-YAP-c-Myc axis may indeed be critical for HIF2α-mediated carcinogenesis[18] and certainly deserves further characterization in NAFLD-associated tumorigenesis because of the central role played by c-Myc in the rewiring of tumor cells metabolism[19] (Figure 1).

The work of Foglia et al[16] also exposed differences in immune and inflammatory markers between tumors arising in Wt and *hHIF2α*$^{-/-}$ mice. In view of this, a detailed characterization of the tumoral immune landscape shaped by HIF2α may be worth carrying out because, as previously mentioned, HCCs emerging on a NAFLD background appear to be more resistant to immune checkpoint inhibitor–based therapies.[4] Moreover, the availability of HIF2α-specific small molecule inhibitors,[20] some of them already in clinical trials

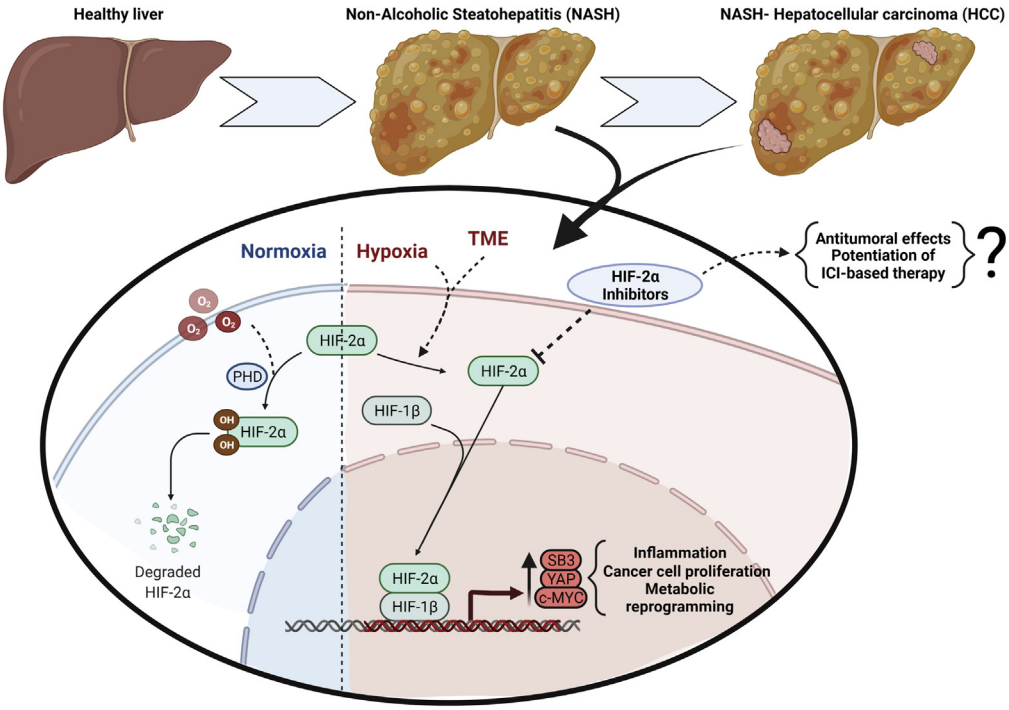

Figure 1. HIF2α is activated early in NAFLD-associated hepatocarcinogenesis and triggers the expression of protumorigenic genes. Pharmacologic inhibition of HIF2α, or of hypoxia-independent tumor microenvironment (TME) signals activating HIF2α, may provide new opportunities to treat HCC or to enhance the efficacy of immune checkpoint inhibitor (ICI)-based therapies. Figure has been created with the BioRender program (BioRender.com).

for other solid tumors (NCT04195750), may enable the direct validation of HIF2α as a therapeutic target in experimental HCC, either alone or in combination with immunotherapeutic strategies (Figure 1). Complementarily, the identification of hypoxia-independent mechanisms for HIF2α activation[8] in the context of NAFLD-HCC might also uncover therapeutic targets upstream of this key factor.

Although these compelling findings warrant further evaluation in additional mouse models that better capture the spectrum of human metabolic syndrome, this study clearly identifies a non-redundant protumorigenic role for HIF2α in NAFLD-related HCC. Intriguingly, it was previously reported that a very high proportion of NAFLD patients show hepatocellular HIF2α overexpression.[12] Therefore, additional "forces" must coexist with HIF2α to trigger liver cancer. Understanding hepatocarcinogenesis in a clinical condition that is reaching pandemic proportions is undeniably of paramount importance.

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