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EDITORIAL

A Novel at*TAK* Against Hepatocellular Carcinoma: Overcoming Resistance to Sorafenib

Despite significant advances in prevention, diagnosis, and therapy, hepatocellular carcinoma (HCC) remains a disease of the utmost significance, being the most common primary liver malignancy and the solid tumor with the second lowest 5-year relative survival rate.[1] For more than a decade, the multiple-target tyrosine kinase inhibitor sorafenib represented the only systemic therapy option for patients with advanced HCC[2] and as yet it is one of the most commonly recommended treatments. Only very recently was the combination of the immunotherapy drug atezolizumab with the angiogenesis inhibitor bevacizumab shown to have a better efficacy than sorafenib.[3] Because sorafenib's long-term clinical benefits are hampered by early development of drug resistance, defining the molecular mechanisms of therapy failure is crucial to the development of novel therapeutic strategies for patients with advanced and refractory HCC.

In the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, Xia et al[4] contribute to this field significantly by describing the role performed by the transforming growth factor-β–activated kinase 1 (TAK1) in driving HCC progression and promoting the acquisition of resistance to sorafenib. TAK1 is a serine/threonine kinase that integrates inputs from several receptors for proinflammatory signaling, including transforming growth factor-β, interleukin 1, and tumor necrosis factor-α, to regulate transcription factors involved in the protection from apoptosis and stemness, including nuclear factor-κB, Activator protein 1, and Yes Associated Protein/transcriptional coactivator with a PDZ binding domain. In a number of preclinical models of solid tumors, TAK1 indeed has been established as a major determinant of resistance to the proapoptotic activity of different anticancer agents (reviewed by Santoro et al[5]).

Sorafenib inhibits tumor growth through a dual mechanism because it acts both on the tumor cells directly and on tumor angiogenesis through inhibition of vascular endothelial growth factor receptor and platelet-derived growth factor receptors signaling. Prior work supported a central role for TAK1 in mediating processes related to tumor angiogenesis.[6] In particular, endothelial-specific deletion of TAK1 leads to embryonic lethality as a result of vascular destruction.[7] TAK1 can prevent endothelial apoptosis and maintain vascular integrity under inflammatory conditions.[8] Moreover, potent proangiogenic factors such as interleukin 8 are among the genes most significantly regulated by TAK1 in cancer.[9] This evidence strengthens the relevance of the findings by Xia et al[4] on the role of TAK1 in the resistance to agents with a strong antiangiogenic activity such as sorafenib.

Ubiquitylation is a key mechanism regulating TAK1 protein levels. K48-linked ubiquitylation of TAK1 blocks TAK1 activation,[10] whereas, K63-linked ubiquitylation of TAK1 sustains its kinase activity in part by allowing its interaction with the TAK1-binding adaptor proteins, resulting in TAK1 autophosphorylation and full enzymatic activation, but also by preventing its proteasome-dependent degradation.[11] In their study, Xia et al[4] identified FBWX2-mediated K48-linked ubiquitylation as a novel mechanism controlling TAK1 protein stability. Xia et al[4] showed in sorafenib-resistant HCC how FBWX2 is degraded by the RNA-binding protein metadherin, which is a prognostic predictor of shorter disease-free survival in HCC patients and a well-known promoter of HCC metastasis.[4] TAK1 protein stabilization is a critical aspect in its signaling because modulation of several downstream targets such as Yes Associated Protein/transcriptional coactivator with a PDZ binding domain often relies on the expression of TAK1, rather than on its own kinase activity.[12]

Collectively, the findings presented by Xia et al[4] pave the path for the development of novel therapies against sorafenib-resistant HCC. Because of its crucial role in different physiological processes including inflammation and immune system homeostasis, the direct targeting of the kinase function of TAK1 poses critical challenges for the development of selective inhibitors that could be responsible for unbearable side effects. Modulation of TAK1 signaling through the reduction of its ubiquitin-dependent stability by interfering with the metadherin/F-box/WD repeat-containing protein 2 axis presents a promising approach for treatment of refractory tumors addicted to the activity of this kinase.

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Conflicts of interest
The authors disclose no conflicts.

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