

EDITORIAL

Targeting CCL2/CCR2 in Tumor-Infiltrating Macrophages: A Tool Emerging Out of the Box Against Hepatocellular Carcinoma



Hepatocellular carcinoma (HCC) is the most frequent primary liver tumor and a leading cause of cancer-related mortality. Unfortunately, the majority of HCC patients present with advanced disease, when locoregional curative strategies are no longer applicable. On the other hand, early, HCCs proved to be resistant to conventional chemotherapies, and drugs targeting specific growth factor signaling pathways tested over the past decade have not succeeded in clinical trials. The molecular heterogeneity of HCCs and the lack of biomarker-based patient stratification strategies may underlie the failure of most of these trials. HCCs usually develop on a background of chronic liver injury and regeneration, inflammation, and fibrosis, features that promote tumor hypervascularity, the other histologic hallmark of this neoplasia. Indeed, the fibrotic and immune microenvironment plays a key role in pathogenic angiogenesis and HCC development and progression. This tenet is supported not only by experimental evidence, but also by the fact that the only therapeutic agents showing clinical efficacy in advanced HCC are those directed toward the interaction of HCC with its microenvironment (ie, anti-angiogenic multikinase inhibitors such as sorafenib, and immune checkpoint inhibitors such as antibodies targeting programmed cell death receptor 1 and its ligand).¹ These observations attest to the potential of targeting the tumor pro-angiogenic and immune milieu for the development of effective anti-HCC therapies. Within the tumor microenvironment, an increased presence of tumor-associated macrophages (TAMs) has been associated consistently with poor patient prognosis. Chemokines play a fundamental role in monocyte recruitment and their maturation into TAMs, cells that have been linked mechanistically to fibrogenesis and angiogenesis development during chronic liver injury and hepatocarcinogenesis.^{2,3} Among the broad family of chemokines, CCL2 (also known as MCP-1) is secreted by most liver cells upon stress and injury, and its only known receptor, CCR2, is expressed in monocytes and liver macrophages. Recent experimental studies have shown that CCL2/CCR2 signaling promotes liver inflammation, fibrosis, and pathologic angiogenesis. Moreover, enhanced CCL2 levels have been linked to a decreased survival rate in HCC patients. Importantly, targeting of CCL2/CCR2 signaling using either small-molecule antagonists, neutralizing antibodies, or RNA aptamer-based inhibitors quells the progression of pathogenic angiogenesis and the growth of subcutaneous HCC xenografts and endogenous liver tumors.²⁻⁵ Together, these findings lend support to the potential application of CCL2/CCR2 and TAM targeting strategies in HCC prevention and treatment. Nevertheless, in

view of the complex role played by macrophages in chronic liver injury and carcinogenesis, including protumoral and antitumoral functions, a detailed understanding of the function of TAMs in this context is warranted.

The study by Bartneck et al⁶ aimed to dissect the TAM subtypes involved in HCC progression, with a particular focus on the role of TAMs mobilized by CCL2/CCR2 signaling in fibrogenesis-driven hepatocarcinogenesis. Interestingly, in resected human HCCs the investigators found a specific accumulation of CCR2⁺ TAMs at the stroma/tumor interface, co-localizing with endothelial cells in areas of intense vascularization. These TAMs did not belong to the suppressive M2-like population, but to an M1 population showing an inflammatory and pro-angiogenic polarization. To grasp the pathogenic significance of CCR2⁺ TAMs in angiogenesis and tumor development, Bartneck et al⁶ applied an RNA aptamer CCL2 inhibitor (CCL2i) in a relevant mouse model of liver fibrosis and hepatocarcinogenesis (diethylnitrosamine plus CCl₄ administration). CCL2 inhibition resulted in reduced TAM1 liver infiltrate and pathogenic angiogenesis, a certain improvement of tissue fibrosis, and a significant inhibition of tumor progression. These findings confirmed the anti-HCC potential of CCL2/CCR2 inhibition observed in previous studies using less clinically meaningful HCC models and highlight the strong impact of CCR2 targeting on tumor-associated angiogenesis. Previous studies in different types of tumors found that M2-polarized TAMs have higher angiogenic potential than the TAM1 population. This is at variance with the observations of Bartneck et al,⁶ who found that TAM co-localizing with newly formed vessels in the chronically injured liver were of the TAM1 type and, most interestingly, that this TAM1 population expressed much higher levels of CCR2. As the investigators discussed, angiogenesis inhibition may indeed be a key aspect of the antitumoral activity of CCL2i. However, the underlying mechanisms, including the observed effects of CCL2i on both TAM1 and TAM2 populations, and the molecular mechanisms of TAM-mediated angiogenesis, still remain to be fully elucidated. The study by Bartneck et al⁶ further supports the notion that CCL2 targeting could be a new strategy against HCC amenable for combination with other efficacious agents such as multikinase and immune checkpoint inhibitors. In fact, CCL2/CCR2 signaling inhibitors are currently being clinically tested for the treatment of nonalcoholic steatohepatitis and liver fibrosis, conditions strongly linked to HCC development.⁵ Interference with CCL2/CCR2 signaling certainly may be effective for the inhibition of established HCC progression. However, given the key role played by the immune system, including macrophages, in cancer surveillance, the application of this strategy

in nononcologic but cancer-prone patients needs careful monitoring.

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Conflicts of interest

The authors disclose no conflicts.



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