Review Article

Slamming hepatocellular carcinoma: targeting immunosuppressive macrophages via SLAMF7 reprograms the tumor microenvironment

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Abstract: Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and one of the leading causes of cancer-related deaths worldwide due to limited treatment options. The tumor microenvironment (TME), which is usually immunosuppressive in HCC, appears to be a decisive factor for response to immunotherapy and strategies aimed at inducing a more inflamed TME hold promise to overcome resistance to immunotherapy. Within the TME, the interplay of various cell types determines whether immunotherapy is successful. Liver macrophages, in particular tumor associated macrophages (TAMs), are known to play a crucial role in tumor progression and represent potential future therapeutic targets. The presence of C-C motif chemokine receptor 2 (CCR2) expressing macrophages is known to be associated with pathogenic angiogenesis and bad prognosis for HCC patients. A recent study published in Cancer Research describes how immunosuppressive macrophages in the TME can be repolarized through targeting Signaling Lymphocyte Activation Molecule Family member 7 (SLAMF7)-regulated CC-chemokine ligand 2 (CCL2) signaling, which sensitizes HCC tumors to immunotherapy in a mouse model. This mini-review gives a brief overview about the current knowledge on SLAMF7 in the context of anti-cancer immunity and how the recent findings could be integrated into new therapeutic strategies for HCC.

Keywords: Hepatocellular carcinoma (HCC); tumor microenvironment (TME); combination therapy; Signaling Lymphocyte Activation Molecule Family member 7 (SLAMF7); tumor-associated macrophages (TAMs)

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Introduction

The growing incidence of cancers, including liver cancer, in recent years has a significant impact on healthcare systems. Hepatocellular carcinoma (HCC) accounts for 75–85% of primary liver cancer and over 800,000 deaths worldwide and shows a constant rise in its prevalence (1). Patients are usually diagnosed at advanced stages of the disease, when therapeutic options become exceptionally limited. In western countries, most HCC cases derive from liver cirrhosis or metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH), while in Africa and eastern Asia viral hepatitis and aflatoxin exposure are responsible for the majority of HCC occurrences (2). Considering that HCC often unfolds following chronic inflammatory liver

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diseases, the tumor microenvironment (TME) appears to be a crucial factor in allowing and supporting tumor progression, as well as in therapy success (3). The TME composition varies amongst HCC patients but includes cellular and non-cellular components. The main cellular components involved are cancer-associated fibroblasts (CAFs), liver sinusoidal endothelial cells (LSECs) and a variety of (often immunosuppressive) immune cells: myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs) and tumor-associated neutrophils (TANs). The various interactions between those cell types are responsible for tumor growth, increased extracellular matrix production, metastasis, angiogenesis and (in-)efficient therapy response (3). Liver fibrosis, the accumulation of extracellular matrix as a repair response following tissue injury, is strongly associated with the progression of HCC. Following liver injury, hepatocytes and immune cells secrete various pro-fibrotic factors responsible for the activation of hepatic stellate cells (HSCs), which differentiate into myofibroblasts and produce excessive amounts of alpha-smooth muscle actin (α-sma) and collagen. LSECs also contribute to liver fibrosis through the release of profibrogenic mediators that further increase HSC activation (4).

The liver also harbors a wide variety of immune cells with the largest proportion being hepatic macrophages. Liver macrophages consist of functionally diverse subsets, mainly the liver resident macrophages, also known as Kupffer cells (KCs), and the monocyte-derived macrophages (MoMFs) originating from the bone marrow (5). KCs represent around 15% of all liver cells, indicating their central role in maintaining liver homeostasis, while the MoMFs population is extremely dynamic and varies depending on the pathological context. Due to their positioning in the sinusoids and their phagocytic activity, liver macrophages play a key role in sensing changes in the liver microenvironment, clearing pathogens and contributing to resolving liver injury (5). Both macrophage populations can embrace pro- or anti-inflammatory polarization states depending on the presence of signals in their microenvironment, such as damaged associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs) or cytokines (6). DAMPs, such as High mobility group box 1 protein (HMGB1) or adenosine triphosphate (ATP) (7), are released from dying cells following liver injury, while PAMPs mostly derive from the gut and reach the liver via the entero-hepatic circulation (8). Moreover, hepatic macrophages interact with other cell types, including hepatocytes, LSECs or other leukocytes, thus contributing to the progression or regression of chronic liver diseases and playing a central role in the regulation of immune responses in HCC (9). Both macrophage populations can give rise to TAMs, which usually display immunosuppressive functions in the TME of HCC and are associated with poor prognosis for HCC patients (10). TAMs show diverse phenotypes: On the one hand, they can adopt a more proinflammatory phenotype when activated by interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), lipopolysaccharide (LPS), or granulocyte-macrophage colony-stimulating factor (GM-CSF), leading to $CD8^+$ T cells recruitment and anti-tumor immunity. On the other hand, when exposed to transforming growth factor (TGF)-β, macrophage colony-stimulating factor (M-CSF), interleukin (IL)-10, and/or IL-13, TAMs exhibit suppressive functions and prevent T helper cell infiltration into the tumor (11). Multiple studies have shown that upregulation of the CC-chemokine ligand 2 (CCL2) in the TME is responsible for the recruitment of a subset of C-C motif chemokine receptor 2 (CCR2) positive macrophages, which accumulate in particular in the highly vascularized surroundings of the tumor (12,13). In mouse models, increased CCL2 excretion also leads to pathogenic angiogenesis and results in an immunosuppressive phenotype of the recruited macrophages. In fact, suppression of the CCL2/CCR2 pathway via a CCR2 antagonist in orthotopic HCC mouse models inhibits infiltration of monocytes and immunosuppressive polarization of TAMs, which results in reduced liver tumor growth (14). Therefore, targeting the CCL2/CCR2 signaling axis appears to be a potential therapeutic strategy to treat HCC.

Current therapies in HCC

Systemic treatments for advanced HCC patients such as the multikinase inhibitors (MKI) sorafenib, lenvatinib, cabozantinib or regorafenib, only grant a small improvement of overall survival (3). Recently, immunotherapies have emerged as effective treatments for HCC. So far, the most efficient immunotherapy for advanced HCC is the use of monoclonal antibodies targeting immune checkpoint molecules like programmed cell death-ligand 1 (PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or pro-angiogenic factors such as vascular endothelial growth factor (VEGF). As such, the combination of tremelimumab (anti-CTLA4) and durvalumab (anti-PD-L1) (15), as well as the combination

of atezolizumab (anti-PD-L1) and bevacizumab (anti-VEGF) (16) have been approved as first line treatments for advanced HCC. Both combination therapies result in a significant survival benefit in comparison to MKI alone (10). Recently, the combination of regorafenib (MKI) with nivolumab [anti-programmed cell death protein 1 (PD-1)] as a first line treatment for patients with non-resectable HCC (RENOBATE trial) also demonstrated efficacy outcomes similar to the atezolizumab/bevacizumab combination (17). However, objective response rates of 15% to 25% (depending on the therapy) mean that the majority of patients are still non-responders and illustrate the need for strategies to increase response rates and overcome tumor resistance to immunotherapy (18).

The role of Signaling Lymphocyte Activation Molecule Family member 7 (SLAMF7) in cancer

SLAMF7, also known as CD319, is a cell surface auto ligand (binding another SLAMF7 molecule expressed by another cell) and was first identified in natural killer (NK) cells where it modulates their capacity to mediate killing of target cells (19). In the presence of the protein adaptor Ewing's sarcoma-activated transcript 2 (EAT-2), SLAMF7 increases the activation of NK cells *in vivo* and *in vitro*, while in the absence of EAT-2, SLAMF7 inhibits NK cell function. This inhibitory effect has also been observed in $CD4^+$ T cells (19). SLAMF7 has also been identified as an immune checkpoint in multiple myeloma (MM), directing the development of novel SLAMF7-targeting therapies such as the SLAMF7 blocking antibody elotuzumab, which increases NK cell mediated cytotoxicity against MM cells via antibody-dependent cellular toxicity and direct activation of NK cells (20). Even though elotuzumab monotherapy did not show efficacy in MM patients, combination with standard-of-care chemotherapies enhanced anti-tumor responses mediated by NK cells and resulted in a significant survival benefit compared to chemotherapy alone (21,22).

The role of SLAMF7 in other cancer types is slowly emerging as well. In ovarian cancer, it was recently demonstrated that SLAMF7 is expressed in tumor infiltrating T cells and that this expression is associated with favorable outcomes for patients and correlates with the infiltration of several other types of immune cells (23). In breast cancer, SLAMF7 overexpression—which is associated with better progression-free as well as disease-specific survival—can be observed in tumor cells, which suggests that treatment with elotuzumab may present a viable option for targeted therapy (24).

In the context of immune cells, SLAMF7 is expressed by mouse and human macrophages and involved in regulating their phagocytic activity both *in vivo* and *in vitro* (25). SLAMF7 interacts with the integrin Mac-1, which aids in recognition of ligands on target tumor cells, thus inducing phagocytosis (25). SLAMF7 has been shown to be upregulated in monocytes and macrophages during sepsis and to be associated with sepsis progression (26). Furthermore, overexpression of SLAMF7 in macrophages is responsible for reduced production of proinflammatory cytokines following toll-like receptor (TLR) stimulation (26).

The role of SLAMF7 in liver diseases and in particular in HCC remains poorly understood as not much is known about SLAMF7 expression in the liver and how this is regulated. In a recent publication, Weng *et al.* studied the potential of repolarizing immunosuppressive macrophages through targeting SLAMF7-regulated CCL2 signaling in order to sensitize HCC to immunotherapy (*Cancer Research*, 2024) (27). The use of transcriptomic databases comparing immunotherapy-responsive and non-responsive HCC patients revealed that the upregulation of SLAMF7 and its presence in patients' serum is associated with a positive response to anti-PD-1 immunotherapy. The authors utilized a hepatocyte specific *Slamf7* knockout strain ($Slamf7^{HKO}$) in order to assess its function in the pathogenesis of HCC in orthotopic mouse models. $Slamf7^{HKO}$ mice developed tumors faster and more spontaneously than wildtype (Wt) mice and exhibited major differences in the HCC immune microenvironment. In-depth analysis of the intratumoral immune cell populations by mass cytometry revealed an increase in macrophage infiltration and a decrease of double-negative T cells ($CD4^-$; $CD8^-$) in $Slamf7^{HKO}$ tumors compared to Wt animals. Furthermore, the authors observed the expansion of an immunosuppressive $Ly6C^{high}$ macrophage population, as well as increased expression of PD-1 on $CD8^+$ T cells for $Slamf7^{HKO}$ mice. These results were corroborated in a cohort of HCC patients, where the expression level of *SLAMF7* is positively correlated to the infiltration of $CD8^+$ T cells and pro-inflammatory macrophages (*Figure 1*). The effect of SLAMF7 on tumor growth appears to be specifically promoted through macrophages as pharmacological inhibition of macrophage populations *in vivo* prevented the SLAMF7 overexpression-induced delay in tumor growth. *In vitro*, co-culture of HCC cells and macrophages demonstrated that the level of SLAMF7 expression by tumor cells is directly correlated with macrophage polarization. When cocultured with

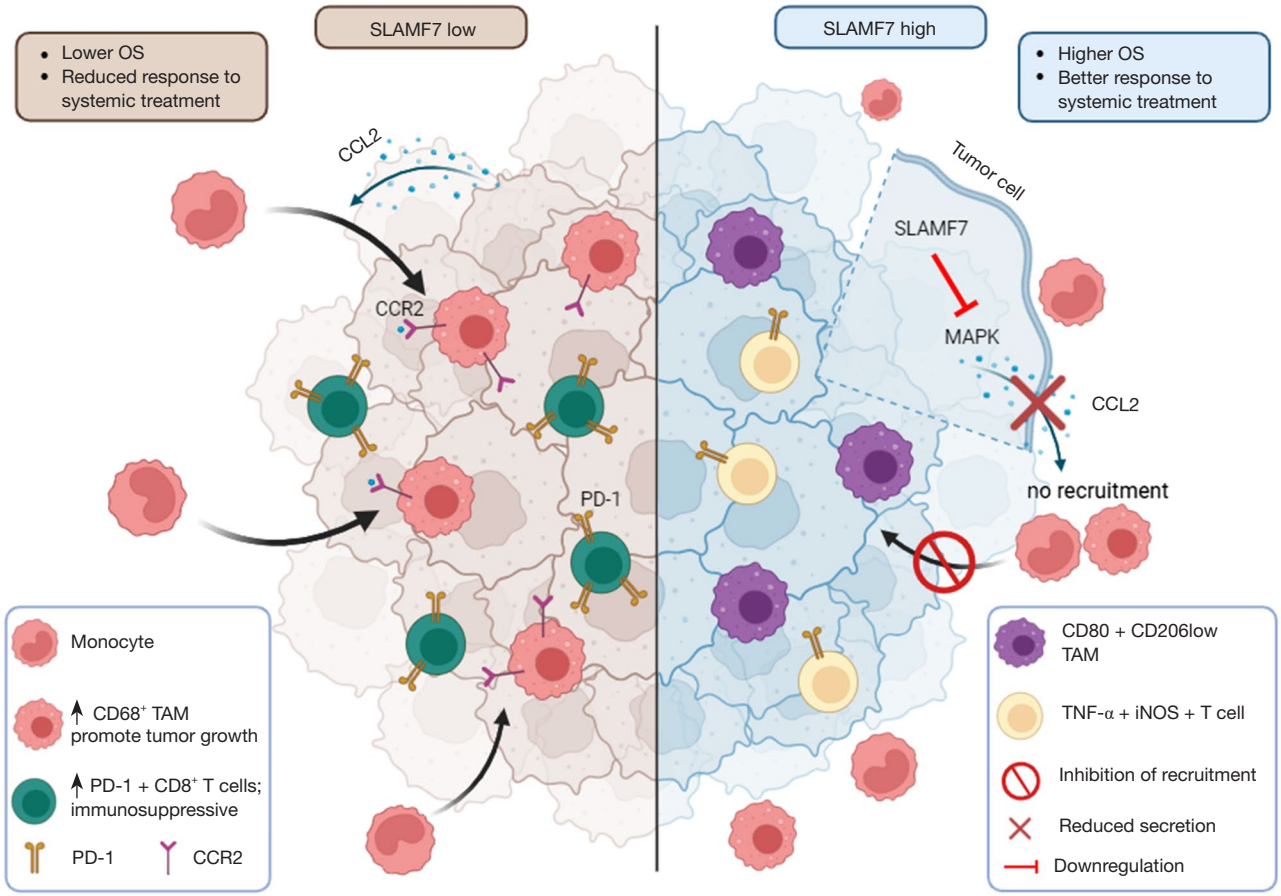

Figure 1 Schematic diagram illustrating the role of SLAMF7 in the tumor microenvironment of hepatocellular carcinoma. When SLAMF7 expression is low (left side), monocytes are recruited to the tumor site via CCL2/CCR2 and differentiate into tumor-promoting CD68$^+$ TAMs. This is associated with high levels of PD-1-expressing CD8$^+$ T cells. In contrast, high SLAMF7 expression (right side) leads to downregulation of the MAPK pathway, resulting in reduced production of CCL2 and inhibition of monocyte recruitment. In this context, both TAMs and CD8$^+$ T cells display a more proinflammatory phenotype, resulting in better tumor control. SLAMF7, Signaling Lymphocyte Activation Molecule Family member 7; OS, overall survival; CCL2, CC-chemokine ligand 2; CCR2, C-C motif chemokine receptor 2; PD-1, programmed cell death protein 1; TAM, tumor-associated macrophage; MAPK, Mitogen-activated protein kinases; TNF-α, tumour necrosis factor alpha; iNOS, inducible nitric oxide synthase. Created with Biorender.com.

SLAMF7-overexpressing tumor cells, macrophages displayed a more pro-inflammatory phenotype with increased expression of the (major histocompatibility complex) MHC-II and several cytokines, and decreased expression of CD206, Arginase 1 and other immune inhibitory molecules.

Translational studies highlighted that low SLAMF7 expression together with high CD68 expression was associated with the lowest overall survival rate for HCC patients, while those displaying high SLAMF7 expression with either high CD80 or low CD206 expression obtained the greatest survival benefit. Besides regulating macrophage polarization, SLAMF7 also seems to reduce macrophage recruitment to the tumor site mediated by a negative regulation of the CCL2 chemokine axis. Indeed, the analysis of the molecular pathways involved showed that upregulation of the Mitogen-activated protein kinases (MAPK) signalling pathway results in increased CCL2 expression and downregulation of SLAMF7. However, when SLAMF7 is strongly expressed in HCC cells, the MAPK pathway is inhibited, and so is CCL2 upregulation.

Finally, Weng *et al.* assessed the efficacy of a combined

treatment using an anti-PD-1 antibody together with blockade of the CCL2/CCR2 axis with an antagonist (RS102895) in mouse models (27). Compared to monotherapy, the combination of RS102895 with anti-PD-1 showed a significant suppression of the tumor growth and decreased metastasis in the lungs. Furthermore, the analysis of the tumor immune landscape by flow cytometry revealed an increase of MHC-II+ macrophage infiltration into the tumor and lower frequencies of $CD8^+PD\text{-}1^+$ T cells. The fact that double negative T cells are decreased in the tumors of $Slamf7^{HKO}$ mice while Slamf7 overexpressing mice display increased MHC-II^+ macrophages and decreased $PD\text{-}1^+$ $CD8^+$ T cells, has not been discussed by the authors. The exact role of these populations and how they influence CCL2 signalling remains an open question and further characterization would be needed to understand how they influence progression of HCC. Importantly, RS102895 treatment was able to rescue the reduced efficacy of anti-PD-1 treatment in mice bearing tumors with $Slamf7^{HKO}$, but had no influence on anti-PD-1 efficacy when SLAMF7 was overexpressed, indicating that SLAMF7 overexpression itself is sufficient to inhibit macrophage recruitment. It would be worthwhile to study the mechanism of action of RS102895 in greater detail. Importantly, a separate study recently demonstrated that targeting SLAMF7 with nanovesicles causes efficient remodelling of the TME and activates robust anti-tumor immunity in murine orthotopic HCC models (28). This suggests that the findings from Weng *et al.* are reproducible in various mouse models and could demonstrate efficiency in a clinical setting (27).

Conclusions

Weng *et al.* elegantly uncovered the molecular mechanisms behind the protective effect of SLAMF7 in HCC tumors (27). Moreover, this study opens the door to new combination therapies for HCC patients, in particular those who do not respond to classical systemic therapy or current immunotherapy. The pharmacological alteration of the TME is an attractive strategy to improve treatments for HCC patients. Nonetheless, some questions remain open: the authors did not comment on the decrease of the double negative T cell population and their potential protective role in patients. In addition, the role of SLAMF7 in NK cells had been highlighted by various studies (23,29), and NK cells can play an essential role in immunotherapies for cancers (30), but have not been studied here. The use of a CCL2/CCR2 antagonist in combination with a PD-1-blocking antibody seems to be promising, however, in other chronic liver diseases such antagonists, e.g., cenicriviroc, have shown very encouraging results in pre-clinical models but failed to show efficacy in clinical phase III trials (31). Therefore, direct targeting of the SLAMF7 pathway may represent a more promising strategy. Future research should investigate additional patient cohorts with different etiologies (e.g., MASH-induced HCC, cirrhosis) and alternative animal models, which better reflect the clinical characteristics of these etiologies (e.g., diet-induced MASH models or chemically induced inflammation with fibrosis/cirrhosis). This would allow to determine whether the beneficial effect of SLAMF7 overexpression represents a general mechanism across HCC etiologies. If so, SLAMF7 might represent a broadly applicable biomarker for immunotherapy response in HCC and could be used for patient stratification. This would be particularly interesting for European and North American cohorts, where MASH-induced cirrhosis is becoming the leading causes of HCC while being associated with particularly low response rates to checkpoint blockade.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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