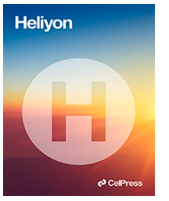
Heliyon 10 (2024) e35338

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

From MASLD to HCC: What's in the middle?

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ARTICLE INFO

Keywords:
MASLD
MASH
Chronic inflammation
Immunity
Immunotherapies
HCC

ABSTRACT

Metabolic dysfunction associated steatotic liver disease (MASLD) is a progressive pathological condition characterized by the accumulation of triglycerides within hepatocytes that causes histological changes, which, in the long run, might compromise liver functional capacities. MASLD predisposes to metabolic dysfunction-associated steatohepatitis (MASH), in which the persistence of inflammatory reactions perpetuates tissue injury and induces alterations of the extracellular matrix, leading to liver fibrosis and cirrhosis. Furthermore, these processes are also fertile ground for the development of hepatocellular carcinoma (HCC). In this latter respect, growing evidence suggests that chronic inflammation not only acts as the primary stimulus for hepatocellular malignant transformation, cell proliferation and cancer cell progression but also reshapes the immune landscape, inducing immune system exhaustion and favoring the loss of cancer immune surveillance. Therefore, a thorough understanding of the cellular and molecular mechanisms orchestrating hepatic inflammatory responses may open the way for fine-tuning therapeutic interventions that could, from one side, counteract MASLD progression and, on the other one, effectively treat HCCs.

1. Natural history of MASLD/MASH

The obesity rate is growing worldwide because of the diffusion of unhealthy lifestyles [1], dragging along a manifold of comorbidities such as dyslipidemia, insulin resistance (IR), type 2 diabetes (T2D), cardiovascular and renal dysfunctions, as well as metabolic dysfunction-associated steatotic liver disease (MASLD) [2]. MASLD is caused by an ectopic fat accumulation within hepatocytes and is generally considered a benign disorder, but it can further progress to an advanced form known as metabolic dysfunction-associated steatohepatitis (MASH). MASH, in turn, is characterized by hepatocellular injury, portal and lobular inflammation, and ductular reaction with or without fibrosis [3,4]. Moreover, MASH can also arise in normal-weight subjects with visceral adiposity [5], a clinical manifestation improperly defined as "lean MASH" with the highest prevalence in Asia and for which still exists conflicting data regarding its aggressiveness as compared to the form occurring in obese individuals [6,7]. Worryingly, the process of MASH progression to liver cirrhosis is regarded as a fertile ground for hepatocellular carcinoma growth (HCC) [8]. However, MASH patients may develop HCC in the absence of cirrhosis, and this makes such a condition possibly even worse because these patients escape from the surveillance for HCC, limiting the possibility of diagnosing tumors in the early stages [9,10]. By now, HCC ranks sixth among

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https://doi.org/10.1016/j.heliyon.2024.e35338
Received 18 April 2024; Received in revised form 4 July 2024; Accepted 26 July 2024
Available online 31 July 2024

commonly diagnosed cancers, but its frequency is expected to increase in the next decades also in relation to an increasing burden of MASLD-related HCCs [11] for which no approved therapeutic options are still available [12,13]. Moreover, HCC-MASH patients are often older and obese, with a higher rate of cardiovascular complications, which strongly limits the therapeutic options compared to patients carrying HCC-related to other causes [10].

2. Inflammatory mechanisms underlying MASLD/MASH pathogenesis

Obesity may induce low-grade chronic inflammation and insulin resistance, which enhance lipolysis, resulting in higher circulating levels of free fatty acids (FFAs) [14]. These metabolic imbalances determine an overflow of FFAs from the blood to the liver, where they accumulate in the form of triglycerides, inducing steatosis. However, the pathogenesis of steatosis may be heterogeneous, involving additional mechanisms unrelated to the metabolic imbalances, which include the genetic predisposition [15,16]. In the long run, the metabolic capabilities of hepatocytes are exceeded, and FFAs cause lipo-toxicity, mitochondrial dysfunctions, oxidative stress, cell injury and death [17,18]. These latter events lead to the release from died/dying cells of multiple molecular mediators collectively regarded as damage-associated molecular patterns (DAMPs), which include nuclear and cytosolic proteins, uric acid, fatty acids, and cholesterol crystals [19] which by the engagement of pattern recognition receptors (PRRs) activate the tissue-resident macrophages known as Kupffer cells (KCs), thus triggering inflammatory responses [20]. Besides that, MASLD is often associated with changes in the composition of intestinal microbiota and with the loss of gut barrier integrity, which can contribute to hepatic inflammation by increasing the translocation of bacterial products through the portal flow to the liver [21]. The persistence of tissue injury and inflammatory responses induces a vicious cycle that may cause the activation of the hepatic stellate cells (HSCs), which differentiating to alpha-smooth muscle actin (α-SMA) myofibroblast-like cells become responsible for collagen deposition and tissue scarring, leading to liver fibrosis and in some cases to cirrhosis [22,23]. In this microenvironment, the combined effect of oxidative stress, DNA damage, regenerative responses, and the exhaustion of immune responses induced by chronic inflammation lay the foundation for the malignant transformation and proliferation of mutated hepatocytes [24–26].

3. Chronic inflammation drives the transition from MASLD to HCC

At the onset of MASLD-related inflammation, the activation of KCs brings to the release of cyto/chemokines that mediate the recruitment of myeloid cells, such as neutrophils and monocytes, from the bloodstream to the liver [27]. Monocytes recruited into the liver differentiate into either monocyte-derived dendritic cells (MoDCs) or monocyte-derived macrophages (MoMFs), which display a pro-inflammatory phenotype characterized by the production of reactive oxygen species (ROS) and cyto/chemokines that promote cell injury, establishing a vicious cycle that amplifies and perpetuates hepatic inflammation, cellular injury, and death [28–31]. Within MASH livers, MoMFs surround dying/dead fat-laden hepatocytes, giving rise to round-shape macrophage aggregates known as hepatic-crown-like structures, the prevalence of which correlates with MASH severity [32]. Recent studies indicate that MASH macrophages have a distinct phenotype characterized by the expression of the triggering receptor expressed on myeloid cells 2 (TREM2), CD9 and the glycoprotein GPNMB, which have been renamed as MASH-associated macrophages (MAMs) [33,34]. These TREM2^{+} MAMs localize within regions characterized by inflammation, cell death, and extracellular matrix remodelling and produce pro-inflammatory cytokines along with pro-fibrogenic mediators such as osteopontin (OPN) and galectin-3 (Gal-3) [34,35]. Noteworthy, the induction of MASH-related inflammatory responses does not involve exclusively immune cells since parenchymal cells participate in this process by producing cytokines [36,37] and molecular mediators, such as the Leukocyte cell-derived chemotaxin 2 (LECT2) generically referred as hepatokines [38,39]. Notably, these hepatokines not only support inflammatory responses but also contribute to the activation of hepatic stellate cells (HSCs) [36,40], predisposing to tissue scarring, fibrosis and cirrhosis, a predominant risk factor for hepatocellular carcinoma (HCC) development [41]. Recent findings also revealed that hepatokines such as Oncostatin M (OSM) may have a role in liver carcinogenesis by influencing relevant biological processes such as angiogenesis and

Table 1
It aims to summarize the main changes to the hepatic immune landscape during the transition from MASLD to HCC. KC, Kupffer cell; DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns, MoMFs, monocyte-derived macrophages; OSAs, oxidative stress derived antigens; MDCSs, myeloid-derived suppressor cells; Treg, regulatory T-cells; TAM, tumor-associated macrophages; NKT, natural killer T cells.

Immunological changes in the transition from MASLD to HCC	
From MASLD to MASH	From MASH to HCC
KC activation by DAMPs/PAMPs and secretion of cyto/chemokines promote the recruitment of myeloid cells [27]	Chronic inflammation and metabolic derangements sustain the expansion of immunosuppressive MDCSs [57–60]
Hepatic recruitment of myeloid cells (e.g., monocytes and neutrophils) [27]	Neutrophils acquire immunosuppressive traits sustaining T-cell exhaustion and Treg differentiation [61,62]
Recruited monocytes differentiate to inflammatory/fibrogenic MoMFs [28–35]	Hypoxia drives the differentiation of immunosuppressive TAMs [63,64]
NK and NKT cell activation/recruitment by metabolic triggers [47]	Lipid accumulation leads to dysfunctional NK and NKT cells, limiting immunosurveillance [65,66]
B-cell activation by PAMPs and OSAs sustain chronic inflammation [45,46]	B-cells differentiate in PDL-1^{+} immunosuppressive plasma cells secreting IL-10 and suppress CD8^{+} T cell functions [67]
Activation of CD4^{+}/CD8^{+} T-cells sustain chronic inflammation [48,51,52]	Chronic antigen stimulation leads to exhausted CD4^{+}/CD8^{+} T-cells [68]

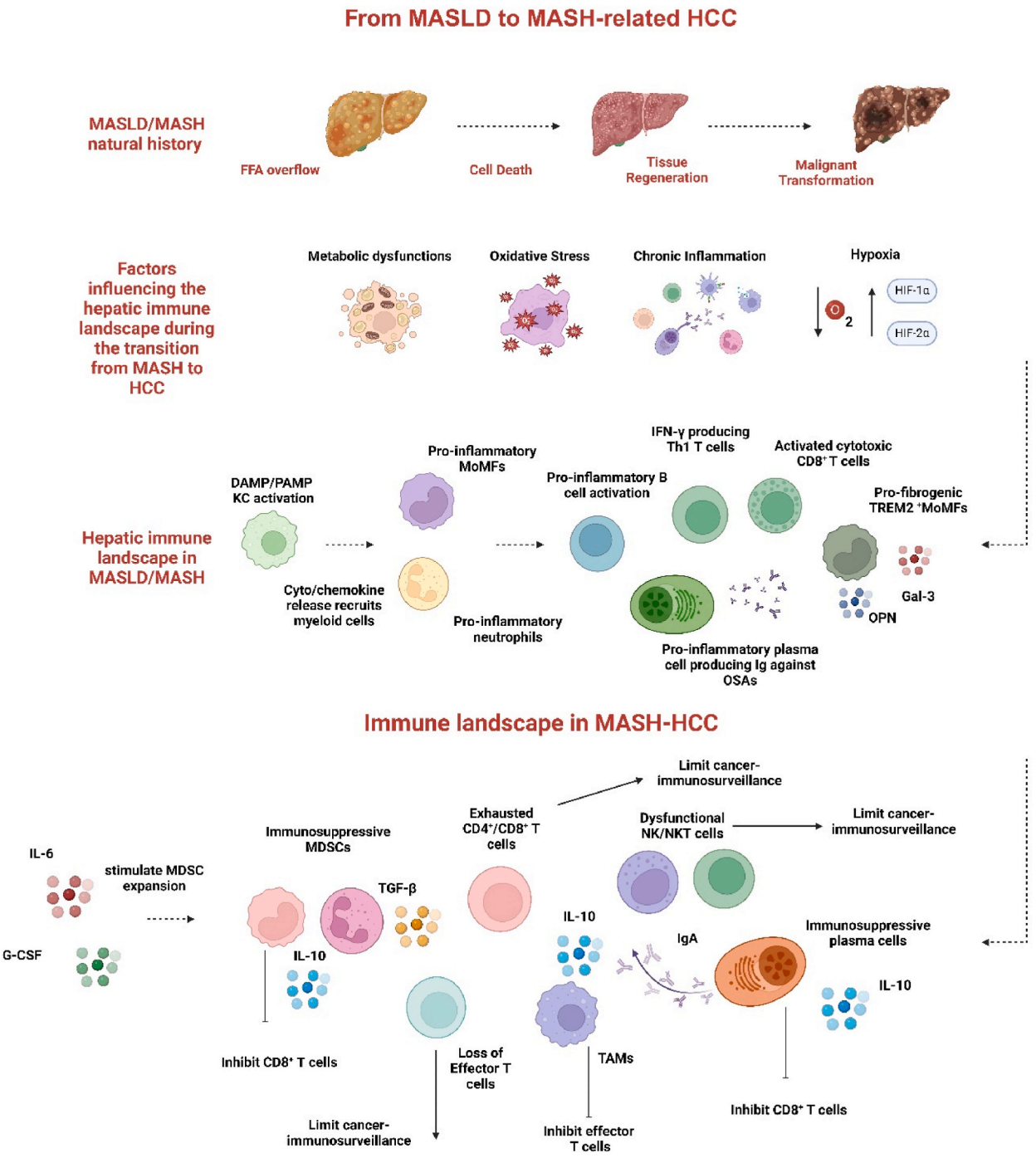

Fig. 1. Overview of the cellular and molecular mechanisms that underlie the transition from MASLD to MASH-related HCC. MASLD-associated metabolic dysfunctions cause oxidative stress, cell death and chronic inflammation. The persistence of inflammatory responses reshapes the hepatic immune landscape with the loss of effector T cells accompanied by an expansion of exhausted T cells, dysfunctional NK/NKT cells and multiple immunosuppressive cell subsets. In parallel, the cytokine milieu undergoes profound modifications because of the predominant production of immunomodulatory molecules. These overall changes lead to a cancer-prone immune microenvironment where transformed malignant hepatocytes can grow undisturbed. FFA, free fatty acid; DAMP, damage-associated molecular pattern; PAMP, pathogen-associated molecular pattern; OPN, osteopontin; Gal-3, galectin-3; OSAs, oxidative stress derived antigens; MDSC, myeloid-derived suppressor cell; TAMs, tumor-associated macrophages. Image created with BioRender.com.

invasiveness [42]. Besides myeloid and parenchymal cells, the inflammatory processes involved in MASLD/MASH progression see the participation of the adaptive branch of the immune system [43,44]. In this regard, B-lymphocytes activated in response to gut dysbiosis and oxidative-stress-derived antigens (OSAs) in the early phase of MASH evolution trigger T-cell mediated responses, sustaining MASH-related inflammatory processes [45,46]. Furthermore, activation of $CD8^+$-T-cells and natural killer T (NKT) cells appears to play a key role in the development of MASH-related HCC [47]. These observations are corroborated by the work of Dudek et al., which have described the presence of MASH-associated metabolically activated "auto-aggressive" $CD8^+$-T cells able to kill hepatocytes independently from the recognition of MHC-class-I-molecules [48]. Interestingly, recent findings also outline that intestinal B cells are not only implicated in the antigen-independent activation of these "auto-aggressive" $CD8^+$- T cells but also sustain the pro-fibrogenic action of MoMFs by IgA-mediated signalling through the FcRγ chain [49]. A further example of the multiple interactions between lymphocytes and MoMFs occurring in MASH emerges from the observation that $CD8^+$ T-cells expressing the co-stimulatory molecule inducible T-cell costimulator (ICOS) can influence the functions of $TREM2^+$ MoMFs by interacting with the ICOS-ligand (ICOS-L) expressed on these cells [50]. Along with this, the MASLD/MASH immunopathology also sees the contribution of differentially activated $CD4^+$ T-helper (Th) cells and innate-like T cells [51–53]. These observations are corroborated by data obtained in mice deficient for T-bet, the master regulator of $CD4^+$ T-cell Th1 differentiation, which develop a mild form of experimental MASH with decreased involvement of multiple immune cell pools such as INF-γ-producing T cells, natural killer (NK) cells and MoMFs [54] (Table 1). Further investigations highlight that oxidative stress can boost hepatic inflammatory responses not only by generating novel antigens but also by compromising regulatory T cell (Treg) viability and functional properties, thus affecting hepatic immune homeostasis and self-tolerance [55]. Recently, Mirshahi et al. described a cancer-prone hepatic immunological pattern in experimental MASH, which sees the predominance of $CD8^+$- on $CD4^+$ T cells and $CD4^+$ Th1-polarized T cells on Th17 and Th2 along with the predominance of NKT cells on NK cells and pro-inflammatory (M1) on anti-inflammatory (M2) macrophages ($CD8^+ > CD4^+$, Th1 > Th17 > Th2, NKT > NK, M1 > M2). They also observed that the presence of an immunological pattern characterized by an equilibrium between differentially polarized $CD4^+$ Th cells (Th1 = Th17 = Th2), NKT cells and NK cells (NKT = NK) and M1 and M2 (M1 = M2) inhibits HCC. Altogether, these results could provide further insights regarding the different susceptibility to HCC found in humans and open the way for defining strategies to establish "healthy" immunological patterns within MASH livers [56].

4. Metabolic derangements, hypoxia, oxidative stress, and chronic antigen stimulation reshape the hepatic immune landscape in MASH-HCC

The transition from MASH to HCC foresees the reshaping of the hepatic immune landscape prompted by metabolic dysfunctions, hypoxia, oxidative stress, and chronic antigen stimulation that gives rise to a unique tumor immune microenvironment (TIME) (Fig. 1). The overall factors gradually transform a pro-inflammatory milieu into an immunosuppressive one through multiple steps, during which differentially activated cell subsets, namely pro-inflammatory and anti-inflammatory, coexist until HCC occurs. Then, immunosuppressive cell populations become predominant but not exclusive since tumor-reactive immune cells, to some extent, persist [69,70]. MASH-associated TIME significantly differs from that of virally driven HCCs and makes the therapies focused on immune checkpoint inhibitors (ICIs) unsuccessful [71–74]. MASH-associated TIME stands out not only for the cellular composition but also for the cellular spatial distribution and for cell-to-cell interactions [75]. However, the cellular and molecular mechanisms that make exclusive MASH-related TIME are still largely unknown [75]. Mechanistically, lipid accumulation within MASH livers causes oxidative stress and the selective loss of $CD4^+$ T-cells, impairs NKT cell anti-tumor immunosurveillance and makes NK cells dysfunctional [65,66,76]. Furthermore, NASH-related TIME sees an expansion of immunosuppressive cell subsets such as myeloid-derived suppressor cells (MDSCs), a heterogeneous population of immature myeloid cells phenotypically resembling either monocytic (M-MDSCs) or granulocytic polymorphonuclear cells (PMN-MDSCs) (Fig. 1) [57]. MDSCs arise under the impulse of chronic low-grade inflammation and metabolic derangements, which stimulate their expansion and recruitment within the liver by IL-6 and granulocyte colony-stimulating factor (G-CSF) mediated signalling [58–60]. MDSDs exert immunosuppressive functions by producing diverse molecular mediators, including IL-10, transforming growth factor (TGF)-β, ROS, nitric oxide (NO), arginase 1 (Arg1) and indoleamine 2,3-dioxygenase 1 (IDO1), among others [77,78]. Spatial proteomics also reveals that MDSCs express the highest amount of the immune checkpoint inhibitor programmed death ligand 1 (PD-L1) and localize in the proximity of exhausted $CD8^+$/$CD4^+$ T-cells [75]. Exhausted T-cells develop within inflamed livers because of the chronic antigen stimulation, which induces a progressive loss of effector functions, proliferation and differentiation while raising the expression of multiple inhibitory receptors, such as programmed cell death protein1 (PD-1) [68] (Table 1). These observations suggest that MDSCs may inhibit T-lymphocytes *via* cell-to-cell crosstalk mediated by the PDL-1/PD1 dyad, contributing to establishing a cancer-prone microenvironment with the cooperation of additional immunosuppressive cells such as tumor-associated macrophages (TAMs) [79]. TAMs develop during the transition from MASH to HCC when the hepatic microenvironment undergoes significant morphological changes promoted by the development of hypoxic conditions. Hypoxia-conditioned cytokine milieu pushes macrophages toward an anti-inflammatory phenotype that characterizes TAMs (Fig. 1) [63,64]. In the same manner, neutrophils acquire immunosuppressive traits and become able to foster the irreversible exhaustion of T cells and induce the differentiation of regulatory T cells [61,62]. T-cell effector functions in MASH-HCC are also inhibited by the expansion of a subset of B cell-derived plasma cells with immunosuppressive properties differentiating under the influence of immunomodulatory molecules like TGF-β [80]. These plasma cells present a phenotype characterized by the expression of IgA and PDL-1 and, by secreting IL-10, contribute to inhibiting cytotoxic $CD8^+$ T cell functions (Table 1) [67].

However, it is mandatory to mention that the above-described factors may also affect liver-resident cell subsets such as hepatocytes, liver-sinusoidal endothelial cells (LSECs) and hepatic stellate cells (HSCs) which, in turn, contribute to modulating immune cell functions, defining the uniqueness of the MASH-TIME [81]. In this regard, hepatocytes play an essential role in modulating immune

responses since they can promote the activation of $CD4^+$/$CD8^+$ T cells by acting as antigen-presenting cells (APCs) but also to drive Treg differentiation with possible implications during carcinogenesis [82]. Hepatocytes also limit the tumor-immunosurveillance modulating the expression of the squalene epoxidase (SQLE), which augments the hepatic production of cholesterol ultimately responsible for the activation of immunosuppressive MDSCs and impairment of cytotoxic $CD8^+$ T cell functions [83]. Besides hepatocytes, LSECs may also exert antigen-presenting and immunomodulatory capacities which support the differentiation of Tregs and inhibit the cytotoxic activity of $CD8^+$ T cells, contributing to the reshaping of the immune landscape during MASH-related carcinogenesis [84–86]. Along with this, emerging evidence suggests that activated HSCs not only differentiate into myofibroblast-like cells supporting liver fibrogenesis, a fertile ground for HCC development but also may have an additional role in conditioning the MASH-TIME [8,81]. In this regard, HSCs foster the expansion of MDSCs and limit the immune responses by restraining cytotoxic $CD8^+$ T cell functions through the expression of high levels of the programmed death-ligand 1 (PDL-1), inhibiting T cell proliferation and increasing T cell apoptosis [87].

These overall changes progressively generate an immunosuppressive microenvironment in which oxidative stress-mediated tissue injury induces regenerative responses involving mutated hepatocytes that proliferate almost undisturbed, leading to HCC growth. In this setting, oxidative stress causes lipid peroxidation, cell injury and the impairment of the immune system but also hepatocyte DNA mutations, which can active oncogenes or inactivate tumor suppressor genes, driving the conversion from hepatocytes to tumoral cells [88].

Finally, we should also mention that MASH may develop because of a genetic predisposition whose presence exacerbates the course of the disease, increasing the susceptibility to HCC [89]. In this regard, a recent study investigating HCC patients found that about 18 % of them showed an amplification in the gene coding for SQLE, suggesting that genetic aberrations may also account for changes in the immune landscape underlying HCC development [90].

5. Concluding remarks and future perspectives

HCC is regarded as an immunogenic tumor since it arises within a chronically inflamed immunological organ, for which it is conceivable to assume a possible beneficial action of immunotherapies [91]. However, immune checkpoint inhibitors (ICIs) are not as effective in MASH-HCC as in viral-driven HCCs [92]. In this respect, the current view sees MASH-related TIME as the Achilles' heel that interferes with ICI-based therapies [93]. Chronic inflammation emerges as the key player in modulating the immune landscape of MASH-HCCs [94]. However, the molecular and cellular mechanisms underlying the MASH-associated TIME are still far from being completely understood. For instance, a still open question concerns the pathogenetic significance of the immune cell spatial distribution within the MASH-HCC microenvironment, which significantly differs from that observed in virally induced HCCs. This difference might explain why MASH-HCC does not respond as expected to the current immunotherapies. A further issue is the poor knowledge of soluble and membrane-bound molecular mediators that coordinate immune cell-cell interactions, sustaining the reshaping of the immune landscape and the loss of cancer immunosurveillance. In addition, the lack of a thorough fine-mapping of tumor-associated antigens (TAAs) strongly limits the possibility of employing cutting-edge therapeutic strategies such as adoptive immunotherapies based on chimeric antigen receptor T cells (CAR-T) and T-cell-receptor modified T cells (TCR-T). In this vein, a comprehensive analysis of TAAs may open the way to the clinical applications of vaccines and adoptive cell immunotherapies in MASH-HCC. Besides this, future investigations should gain further insights into the molecular mechanisms that influence the immune composition, spatial distribution, and cell-to-cell interactions within MASH-HCC, that is an aspect of MASH-HCC pathogenesis still rather obscure. Gaining further insights into this matter may allow the fine-tuning of target therapies, for instance based on nanotechnologies, which are already employed with success in other inflammatory contexts [95]. The immune system shows high plasticity and can undergo phenotypical and functional changes in response to a dynamic environment [96]. Therefore, theoretically, it is conceivable to imagine therapeutic strategies for re-activating the immune system and reestablishing cancer immunosurveillance as a treatment for MASH-HCC. To this aim, functionalized nanoparticles (NPs) may represent a valuable tool for targeting selectively specific cell subsets with bioactive molecules under a controlled release. Accordingly, future studies may aim to fine-tune drug-loaded functionalized NPs to affect the TIME by disrupting inhibitory immune cell-cell interactions and boosting the immune system against tumoral cells to restore cancer immunosurveillance.

Data availability statement

No data was used for the research described in the article.

Funding

This study was supported by the research grant IG 27154 (Associazione Italiana Ricerca sul Cancro, Milano Italy)

CRediT authorship contribution statement

Alessia Provera: Writing – original draft, Conceptualization. **Cristina Vecchio:** Writing – original draft, Conceptualization. **Anteneh Nigussie Sheferaw:** Writing – original draft. **Ian Stoppa:** Conceptualization. **Deepika Pantham:** Conceptualization. **Umberto Dianzani:** Writing – review & editing, Conceptualization. **Salvatore Sutti:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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