International Immunopharmacology 73 (2019) 10–16

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

Natural killer cells involved in tumour immune escape of hepatocellular carcinomar

Chen Han[a], Yongjie Jiang[b,1], Zhaoxia Wang[a], Hengxiao Wang[a,*]

[a] Department of Pathology, Institute of Basic Medicine, Shandong Academy of Medical Sciences, Jinan 250062, China
[b] The First Affiliated Hospital of Xinxiang Medical University, Xinxiang 453003, China

ARTICLE INFO

Keywords:
Natural killer cells
Hepatocellular carcinoma
Immune escape

ABSTRACT

Natural killer cells are the first line of host immune surveillance and play major roles in the defence against infection and tumours. Hepatic NK cells exhibit unique phenotypic and functional characteristics compared to circulating and spleen NK cells, such as higher levels of cytolytic activity and cytotoxicity mediators against tumour cells. However, the activities of NK cells may be reversed during tumour progression. Recent studies demonstrated that hepatic NK cells were exhausted in hepatocellular carcinoma (HCC) and exhibited impaired cytolytic activity and decreased production of effector cytokines. The present review discusses current knowledge on the role of exhausted NK cells in promoting HCC development and the mechanisms contributing to tumour immune escape, including an imbalance of activating and inhibitory receptors on NK cells, abnormal receptor-ligand interaction, and cross-talk with immune cells and other stromal cells in the tumour environment. We provide a fundamental basis for further study of innate immunity in tumour progression and serve the purpose of exploring new HCC treatment strategies.

1. Introduction

Hepatocellular carcinoma (HCC) is a common high-malignancy tumour that exhibits an insidious onset, invasive fast-growing characteristics, and a high recurrence rate and fatality [1,2]. Combined chemotherapy and radiotherapy are primarily used, but this treatment exhibits limited effect on advanced HCC, and the invasion and transfer into neoplasm are the primary causes of death in HCC patients [3–5]. The surveillance function of the immune system plays a critical role during the early stages of the tumour, but disorders of the immune system and tumour microenvironment may be involved in the immune escape of the tumour [6]. Natural killer (NK) cells are innate immune cells that play extremely important roles in the immune surveillance of tumours. NK cells are the first line of defence against tumours and suppress tumour growth via cell infection, direct cytotoxicity via the release of cytolytic granules and cytokine secretion, or indirectly via the orchestration of anti-tumour immune responses without the recognition of tumour-specific antigens [7–9]. The liver is a unique organ of predominantly innate immunity, and it contains a large lymphocyte population. The percentage of hepatic NK cells and their toxicity are much higher than cells in the spleen or peripheral blood of healthy controls [10,11]. Hepatic NK cells play a critical role in immune surveillance in the normal liver, but exhaustion and dysfunction of NK cells are involved in the progression of HCC. The present review summarizes the potential mechanisms of HCC tumour escape via NK cell exhaustion, including abnormal NK cell phenotype, the recognition mechanism of ligand-receptors, killing dysfunction, and the cross-talk effect with other immune cells, to provide novel ideas on the immunotherapy of NK cells.

2. Natural killer cells

NK cells are a heterogeneous population of the innate lymphoid cell (ILC) family [12,13] that play an important role in host defence against microbial infections and tumours [14]. NK cells exhibit an inherent capacity to kill tumour cells without prior sensitization and participate in a wide variety of immune responses via the production of inflammatory cytokines, such as interferon-gamma (IFN-γ), which influences adaptive immune cells [15]. Human NK cells are phenotypically characterized by $CD56^{+}CD3^{-}$ expression and the expression levels of CD56 [16]. NK cells are further subdivided into two subsets, $CD56^{bright}CD16^{dim}$ and $CD56^{dim}CD16^{bright}$ NK cells [17]. Approximately 90% of peripheral blood and spleen NK cells are $CD56^{dim}CD16^{bright}$ NK cells that exhibit higher amounts of cytolytic

* Corresponding author.
E-mail address: Wanghengxiao@aliyun.com (H. Wang).
[1] Co-First Author.

https://doi.org/10.1016/j.intimp.2019.04.057
Received 29 November 2018; Received in revised form 21 March 2019; Accepted 25 April 2019
Available online 09 May 2019

granules, such as perforin and granzyme [18], and $CD56^{bright}CD16^{dim}$ NK cells are immune regulatory and constitute the majority of NK cells in secondary lymphoid tissues, where they produce abundant cytokines, such as IFN-γ, tumour necrosis factor-beta (TNF-β), tumour necrosis factor-alpha(TNF-α), and granulocyte macrophage-colony stimulating factor (GM-CSF), but exhibit weaker cytotoxicity [19].

3. Hepatic NK cells

The liver is a unique immune organ that contains a large number of innate immune cells, such as Kupffer cells, NK cells, NKT cells and γδT cells [20]. The range of lymphocytes present in the liver differs markedly from the peripheral blood and other organs [21]. NK cells are enriched in the liver and account for 25%~40% in human and 10%~20% in mouse of the total intrahepatic lymphocytes, which are far greater than the proportion of NK cells in peripheral blood of approximately 5%~10% [22]. NK cells in the liver are preferentially situated in the hepatic sinusoids, often adhering to the endothelial cells [23]. More studies suggest that the NK cells in the liver, which are known as hepatic NK cells, exhibit different immunophenotypical, morphological, and functional characteristics than peripheral NK cells. NK cells in most human peripheral circulation are $CD56^{low}CD16^{+}$ cells that kill target cells and produce cytokines. $CD56^{hi}$CD16 NK cells are the main NK cell subsets in liver, and to produce a large number of cytokines under the stimulation of proinflammatory cytokines [24]. The mouse liver-resident NK cells express high amounts of CD49a, CXCR6, and CD69, are efficient producers of IFN-γ and TNF, and can produce relatively high amounts of granulocyte macrophage colony-stimulating factor (GM-CSF) and CCL3 [25]. Moreover, liver-resident NK cells express high amounts of TRAIL and are capable of inducing cell death in TRAIL-sensitive target cells. By producing IFN-γ, TNF, and GM-CSF and high expressing TRAIL stimulating by target cells. Hepatic NK cells exhibit greater cytotoxicity levels against tumour cells and express higher levels of cytotoxicity mediators compared to peripheral NK cells [24,26–28].

4. Activating and inhibitory receptors of NK cells

The cytotoxicity of NK cells against target cells is dependent on the delicate balance between the effects of the inhibitory and activating receptors expressed on NK cells [29,30]. Activating receptors are essential elements in the regulation of NK cell function. The dominant activating receptors on NK cells include NKG2C, NKG2D, signalling lymphocytic activation molecule (SLAM) family molecule 2B4 (CD244), the DNAX accessory molecules (DNAM-1, CD226), and the natural cytotoxicity receptors (NCRs)(NKp30, NKp44, NKp46 and NKp80) [31–34]. The binding of activating receptors to its ligands is indispensable to the NK cell killing of infected cells and tumour cells. Various inhibitory receptors are also expressed on NK cells, such as killer cell immunoglobulin-like receptors (KIRs), CD94/NKG2A and leukocyte immunoglobulin-like receptor 1(CD85) [35,36]. These numerous receptors make NK cells a valuable and versatile element and an alternative to T cells for antitumour immunotherapy. NK cells exhibit an inherent capacity to kill tumour cells without prior sensitization, and they are also involved in a wide variety of immune responses via the production of inflammatory cytokines. NK cells exert an immediate cytotoxicity upon encountering a malignant cell via the production of cytokines, such as IFN-γ, and the release of cytotoxic granules to directly kill target cells [37].

5. Tumour-associated NK cell exhaustion in HCC

NK cells exhibit strong cytotoxic capacity against tumour cells, but tumour cells and the tumour microenvironment develop several mechanisms to produce the exhaustion of NK cells and protect tumour cells against NK cell-mediated attack [38–40].NK cells failure to eliminate or control transformed cells allows surviving tumour cell variants to grow in an immunologically unrestricted manner.

Several studies demonstrated that the percentage and subsets of NK cells in the liver were transformed significantly into the development and progression of HCC. Cai L et al. found a significant reduction of the total proportion of peripheral NK cell compartments in HCC patients with different disease stages compared to healthy subjects, especially a decrease in peripheral $CD56^{dim}CD16^{pos}$NK cell subsets and increase in circulating $CD56^{bright}CD16^{neg}$ NK cells. A dramatic reduction of $CD56^{dim}CD16^{pos}$NK cell subsets was also observed in tumour regions compared to non-tumour regions in these HCC patients. These tumour-infiltrating $CD56^{dim}$NK cells also exhibited severe impairments in IFN-γ production and cytotoxicity [41]. Gao et al. [42] examined HBV-related HCC patients and observed that the frequencies of $CD56^{dim}$ NK cells were significantly lower in tumour compared to the corresponding para-tumour tissues. The ratio of $CD56^{bright}$ NK/$CD56^{dim}$ NK subsets was decreased in the tumour, and the $CD56^{bright}$ NK subset was reduced more obviously than the $CD56^{dim}$ NK subset. The frequencies of $CD38^{+}CD56^{dim}$, $NKG2A^{+}CD56^{dim}$ and $NKG2D^{+}CD56^{dim}$NK subsets were also lower in tumour-infiltrated lymphocytes (TILs). The downregulation of CD38 and NKG2D on $CD56^{dim}$ NK cells suggested that the activation of liver-resident NK cells was suppressed in tumour compared to para-tumour tissues in HCC patients [43].

Human NK cells are also further divided into four functionally distinct subsets based on the surface density of CD27 and CD11b: $CD11b^{-}CD27^{-}$(DN), $CD11b^{-}CD27^{+}$($CD27^{+}$SP), $CD11b^{+}CD27^{+}$(DP) and $CD11b^{+}CD27^{-}$($CD11b^{+}$SP) [44], which represent the four stages of NK cells from immaturity to maturity. The percentage of liver-infiltrating DN NK cells from tumour tissue increased significantly compared to adjacent non-tumour tissue and control livers, and the percentages of liver-infiltrating $CD11b^{+}$SP and DP NK subsets were markedly decreased. The expression of activating receptors (NKG2D, NKp30 and CD226) and inhibitory receptors (NKG2A, KIR2DL2/DL3/DS2 and KIR3DL1/DS1) in DN NK subsets was downregulated compared to the other three subsets, especially the $CD11b^{+}$SP population. A downregulation of CD2, CD7, CD57 and CD11c, which are expressed on highly mature NK cells, was observed on DN NK cells compared to the other three subsets. An upregulation of CD117 and CD127, which are typically expressed on immature NK cells, was observed on DN NK cells compared to the other three subsets. Therefore, DN NK subsets within tumour tissues exhibit an inactive and immature phenotype, which suggests an impaired function of these subsets. DN NK cells exhibited significantly reduced CD107a expression and IFN-γ production compared to the other three subsets and decreased tumour-infiltrating NK cells (TINK) degranulation and cytokine production. Collectively, the substantial presence of DN NK subsets in TINK cells with deficient function contributes to the dysfunction of TINK cells in HCC patients [45].

6. Impaired NK cells are involved in tumour immune escape

The tumour-induced microenvironment favours tumour escape from NK cell-mediated cytotoxicity via two main mechanisms: imbalances between killing activity receptors and killing inhibitory receptors on NK cells inhibits the effects of NK cell function; and tumour cells also self-modify via the selection/editing of poorly immunogenic antigens to evade NK cells detection or destruction [46].

Reduction of MHC class I by certain cancer cells may be perceived as a “missing self” by the inhibitory receptor KIRs on NK cells, which generally interacts with the MHC class [47]. However, a reduction or loss of MHC class I is rarely sufficient to trigger NK cell-mediated lysis because NK cell activation and killing activity are regulated via the binding of activating and inhibiting receptors with their related ligands. Tumour cells may exploit various strategies to compensate for the losses, such as the downregulation the membrane ligands or an upregulation of soluble ligands or killing inhibitory receptor-related ligands

(KIRs-L). These factors allow tumour cells to escape immune control and lead to the appearance of an overt tumour.

6.1. NKG2D and its ligands

A critical mechanism of NK-mediated recognition of target cells is via the NKG2D [48,49]. NKG2D is a homodimeric activating receptor and member of the C-type lectin superfamily that is encoded by the KLRK1 (killer cell lectin-like receptor subfamily member 1) gene [50]. NKG2D is constitutively expressed on the surface of all NK cells, but it is also expressed on invariant NKT cells and subsets of T cells, including $CD8^+\alpha/\beta$T cells and γ/δT cells. The binding of NKG2D ligands induces phosphorylation of a Y-X-X-M motif on the cytoplasmic tail of DAP10 [51], which activates NK degranulation and the killing of target cells. The activation of NK cells via NKG2D also triggers the production of cytokines, including IFN-γ, GM-CSF, and MIP-1β [52,53]. Therefore, NKG2D is a major recognition receptor for the detection and elimination of infected and transformed cells [54–56].

Ligands of the human NKG2D receptor primarily include the MHC I-related molecules MICA/B and the UL16-binding proteins (ULBP-1 to ULBP-6) [57]. These ligands are rarely expressed in healthy tissues, but production is induced during various cellular stresses, such as DNA damage, heat shock, or cellular transformation. Prior studies established that the expression of NKG2D ligands on tumour cells produced a very rapid immune response, particularly by NK cells, and renders these susceptible to killing tumour cells [58].

MICA proteins exist in two forms, membrane and soluble MICA (mMICA and sMICA). MICA and MICB are expressed on a subset of human hepatocellular carcinoma tissues and are involved in hepatoma cell sensitivity to NK cells [59]. A reduction in the predominant membrane-bound MICA/B in hepatocellular carcinoma is associated with the progression of HCC early stage (T1 and T2) but not middle-late stage (T3 and T4) [60]. Fang et al. examined GRP78, which is a molecular chaperon involved in the folded protein response (UPR) that reduces the accumulation of unfolded cellular proteins and restores normal ER function. GRP78 was increased in hepatoma tissues and negatively correlated with MICA/B expression levels via post-transcriptional regulation [61]. The mMICA is created when the combination of the integrin metalloprotease 9 (ADAM9) separates from the intracellular and extracellular binding sites, which results in the partial loss of the MICA cellular domain and the formation of sMICA [62,63]. High levels of sMICA increased the incidence of portal venous tumour emboli, induced NKG2D internalization and degradation, and affected the antitumour activity of NK cells in HCC patients. Our previous study also indicated that tumour cells escaped the immunosurveillance of NK cells because of MICA reduction in an HCC-bearing xenograft mice model [64].

ULBPs are another NKG2D ligand that effectively increase NK cell cytotoxicity and promote the secretion of numerous cellular factors, such as IFN-γ and TNF-α, in humans [65]. ULBP-positive tumour cells are more susceptible to killing by NK cells than ULBP-negative tumour cells. The ULBP family is composed of at least six members (ULBP1-6), and the abnormal expression of several numbers was found in HCC in vitro and *vivo*. Mou et al. [66] demonstrated that ULBP3 was overexpressed on tumour cell lines and tissues, and ULBP1 was expressed predominantly in tumour cells but not poorly differentiated HCCs (poor-HCC) [67]. These studies demonstrated that the reorganization ability to tumour cells of NK cells via the NKG2D receptor gradually weakened with the development of HCC, and NKG2D ligand expression was associated with tumour eradication and superior survival.

6.2. NKG2A and HLA-E

Another hallmark of liver NK cells compared to NK cells in peripheral blood is the expression of the inhibitory receptor natural killer group 2 member A (NKG2A/CD94). Sun et al. [68] found that the expression ofNKG2Ain NK cells was significantly increased in HCC intratumour tissues. These NK cells, particularly $CD56^{dim}$ NK cells with higher NKG2Aexpression, exhibit features of functional exhaustion and are associated with a poor prognosis. They also found that the increasing expression ofNKG2A may be induced via IL-10, which is a critical immunosuppressive factor charged with maintaining the tolerogenic environment of the liver, and it was highly expressed in the plasma of HCC patients. Previous studies demonstrated that IL-10 played a key role in the growth and/or differentiation of NK cells [69], and IL-10 in the liver may contribute to the lower functional capacity of liver NK cells, including lower IFN-γ production and the decreased proportion of Ly49-expression NK cells [70].

Tumour cells play a more active role in subduing immunity via the expression of inhibitory ligands that prevent intimate contact and inhibit the cytotoxic actions of NK cells. The natural ligand of NKG2A/CD94 is HLA-E, which is a non-classical HLA class I molecule that is expressed on the cell surface of most leukocytes and transformed cells, including virus-infected cells and tumour cells [71,72]. Upregulated HLA-E expression was observed in HCC tissues compared to adjacent non-tumour liver tissues and normal livers from HCC [73], and reduced HLA-E expression of intratumour regions correlated with longer overall and disease-free survival in HCC patients [68]. Therefore, blockade of the NKG2A/HLA-E pathway may restore immunity against HCC via the reversing of NK cell exhaustion.

6.3. DNAM-1 and its ligands

Tumour cells initiate an intrinsic response to cellular stress, which results in the aberrant expression of DNAM-1Ls, analogous to the induction of NKG2D ligands [54].DNAM-1 (DNAX accessory molecule-1) is a protein encoded by the CD226 gene in humans, which is a transmembrane glycoprotein involved in NK cell cytotoxicity. Ligands of DNAM-1 (CD226) are the nectin-like molecules CD112 and CD155 (also known as PRR2 and PVR), and DNAM-1 is a pivotal regulator of NK cell-mediated functions against target cells, such as cancer, viral infections and immune-related pathologies [74]. CD155 is a transmembrane glycoprotein, and the external domain mediates cell attachment to the extracellular matrix molecule vitronectin, which is the most important ligand in DNAM-1-mediated recognition and cytotoxicity. Qu et al. [75] demonstrated decreased CD155 expression in HCC tissues compared to adjacent non-cancerous tissues. The loss of CD155 expression was associated with higher serum a-feto-protein (AFP) concentrations. Gong et al. [76] further demonstrated that activated unfold protein response (UPR) attenuated the sensitivity of human hepatocellular carcinoma cells to NK cell cytotoxicity by decreasing CD155 expression levels in HCC patients. HCC progression is often accompanied with hypoxia, reduced glucose supply, and increased UPR in the tumour microenvironment [77]. They revealed that activating transcription factor 6 (ATF6) and inositol-requiring enzyme-1α (IRE-1α) pathways, which regulate UPR, were involved in the regulation of CD155 expression in hepatoma cells. The IRE-1α pathway also contributed to the increased expression of the ER-associated degradation (ERAD)-related molecule HRD1 and facilitated CD155 degradation. These findings suggest that the downregulation of CD155 expression is an immune evasion strategy of HCC.

7. Crosstalk between immune cells and NK cells in tumour microenvironment

The liver tumour microenvironment (TME) is a complex mixture of tumoural cells within the extracellular matrix (ECM) in combination with a complex mix of stromal cells and proteins. The TME contains various cell types, such as angiogenic cells, immune cells, and cancer-associated fibroblastic cells, that interact and create a dynamic network of a permissive environment for HCC initiation and progression [78]. The activity of NK cells in the TME may be constrained because of the

crosstalk and interaction between different immune cells and NK cells.

7.1. Tumour-associated macrophages (TAMs)

Macrophages are a type of leukocyte with antigen-presentation capacity (APC). These cells are actively involved in tissue remodelling, phagocytosis and the scavenging of foreign substances and cellular debris [79]. Macrophages in the tumoural region are termed TAMs [80]. Solid tumours recruit an abundance of immune cells into the TME, and macrophages may account for up to 50% of the tumour mass [81]. Increasing numbers of studies demonstrated that TAMs played a major role in tumour cell proliferation, angiogenesis, metastasis and invasion [82]. TAMs also express/release immunoregulatory factors that directly inhibit NK cell function [83]. Wu et al. [84] demonstrated that monocytes/macrophage ($CD68^+$cells) and NK cells often accumulated in peritumoural stroma rather than intratumoural areas. High infiltration of peritumoural stroma monocytes/macrophages positively correlated with impaired functional activities of NK cells and lead to NK cell exhaustion/reduction in the intratumoural region. NK cells exposed to tumour-derived monocytes underwent revision from active to exhaustion. Monocytes from HCC tissues strongly express CD48 proteins, and the dysfunction of NK cells induced by monocytes was markedly attenuated by blockade of the CD48 receptor 2B4 on NK cells, but not blockade of NKG2D or NKp30.

7.2. Myeloid-derived suppressor cells (MDSCs)

MDSCs are a heterogeneous population of myeloid cells, including macrophages, granulocytes, and other cells, that express Gr-1 and CD11b in mice. Recent studies demonstrated that MDSCs were recognized as a subset of innate immune cells that altered adaptive immunity and produced immunosuppression [85–87]. MDSC expansion is one mechanism that HCC tumours develop to evade the host immune response in mice and human [88]. A new population of MDSCs, labelled CD14(+)HLA-DR(-/low), were significantly increased in the peripheral blood and tumour tissues of HCC patients. MDSCs from HCC patients inhibited autologous NK cell cytotoxicity and cytokine secretion when cultured together in vitro. The inhibitory effect of MDSCs on NK cells only occurred when the two types of cells were directly exposed and survived longer. Further study demonstrated that MDSC-mediated inhibition of NK cell function was primarily dependent on the NK-activating receptor NKp30, which is one of the three natural cytotoxicity receptors responsible for the NK cell-mediated lysis of autologous immature dendritic cells [89].

7.3. Cancer-associated fibroblasts (CAFs)

CAFs are one of the most prominent cell types of the stromal compartment in the tumour microenvironment (TME), which are embedded in the fibrillar matrix of the connective tissue and play a critical role in the modulation of neighbouring cells [90,91]. CAFs affect tumours via the secretion of several factors, such as chemokines, vascularization-promoting factors VEGF and PDGFs, and the growth factor EGFs, which promote tumour initiation, invasion, angiogenesis, and metastasis, and regulate immune evasion [92,93]. CAFs may influence the HCC progression because HCC tumours initially arise in the context of cirrhosis, in which the amount of activated fibroblasts is impressive [94–96]. Previous studies demonstrated that CAFs increase the suppression of NK cell killing activity in the TME [97]. T. Li et al. [98] demonstrated that HCC-associated fibroblasts from tumours and non-tumour cirrhosis tissues exhibited an activated phenotype and produced significant levels of suppressive mediators, including PGE2 and IDO, which lead to the dysfunction of NK cells. CAFs also directly secrete some immunosuppressive factors, such as TGF-β. Previous studies demonstrated that TGF-β potently inhibited the proliferation of most cells types, including endothelial cells, haematopoietic cells, and lymphocytes, and it is known as a tumour suppressor [99]. TGF-β signalling exerted a suppressive role in the proliferation of premalignant hepatocytes and HCC cells [100]. Sui et al. [101] demonstrated that TGF-β was an important factor that induced immunosuppressive effects on NK cytolytic ability in HCC, and neutralized the significant increase in the cytolytic ability of NK cells. These findings provide novel insights into the mechanisms by which CAFs perform a suppressive role in HCC via the induction of NK cell dysfunction, and the inhibition of CAFs may contribute to the recovery of NK cell activity in HCC therapeutics.

7.4. Dendritic cells (DCs)

DCs are uniquely well-equipped professional antigen-presenting cells that play a key role in the TME. Cross-talk between NK cells and DCs plays a major role in immune responses [102] and leads to the triggering of NK cell survival, differentiation, cytotoxicity and IFN-γ secretion directly via the secretion of cytokines, such as IL-12 and IL-15 [103]. Yamamoto et al. [104] investigated the immunoregulation of NK cell activity and DC function by a-fetoprotein (AFP), which is a tumour-associated antigen in HCC. They demonstrated that high levels of AFP produced by HCC tissues impaired NK activity via inhibition of IL-12 production by DCs. Zhou et al. [105] demonstrated that DCs stimulated by TLR7 and/or TLR8 agonists enhanced NK cell-mediated anti-hepatocellular carcinoma. They found that the stimulation of TLR7/8 signalling induced maturation of DCs, which was accompanied by high expression of co-stimulatory molecules (CD1a, CD11c, CD83 and CD86) and the secretion of pro-inflammatory cytokines, which may contribute to the crosstalk between DCs and NK cells. DCs assist in the function of NK cells via cell-to-cell contact and cytokine secretion (IFN-α/β, IL-12, IL-15 and IL-18), which results in the enhanced activation of NK cells and increased cytolysis of NK cells against HCC cells.

Reciprocally, NK cells have also been shown to play immunoregulatory “helper” roles, by activating DCs and enhancing stimulating Th1 and cytotoxic T lymphocyte (CTL) responses, respectively [106]. DC1, which induced by NK cells or NK cell-related soluble factors and characterized by high capacity to produce IL-12p70 in response to subsequent interaction with Th cells, are resistant to tumour-related suppressive factors, and show an enhanced ability to induce Th1 and CTL responses [107,108]. However, impairment of NK cells in advanced HCC affects the maturation and function of DCs. Masahisa et al [109]. demonstrated that NK cells augment the immune stimulatory capacity of DC in an NKG2D-dependent fashion and that sMICA-mediated down-modulation of NKG2D results in impairment of DC functions. They found that NK cells upon stimulation of human hepatoma cells induced maturation of DC and enhanced the allostimulatory capacity of DC; maturation and activation of DC was completely abolished when NK cells were pretreated with sMICA-containing serum. Therefore, strategies that stimulate DC-NK crosstalk may reverse the impaired interaction between NK cells and DCs because of the immunosuppressive TME and enhance the efficacy of tumour immunotherapies.

8. Summary

Hepatic NK cells in HCC patients or hepatoma-bearing mice are unable to recognize and kill tumour cells because of a variety of factors, such as altering the ligands expressed on the surface of tumour cells, inhibition of cytokine secretion, and interactions between immune cells in the tumour microenvironment, in which the activity of NK cells is negatively regulated (Fig. 1.). Restoration and augmentation of NK cell cytotoxic functions in the TME are important strategies to overcome immunosuppression and eliminate the tumour. The identification of methods to increase the percentage and absolute number of circulating NK cells, including spleen NK cells and peripheral NK cells, recruit these cells to the liver, or stimulate the liver to enhance the activity of hepatic NK cells, is of great significance for the immunotherapy of HCC. Various

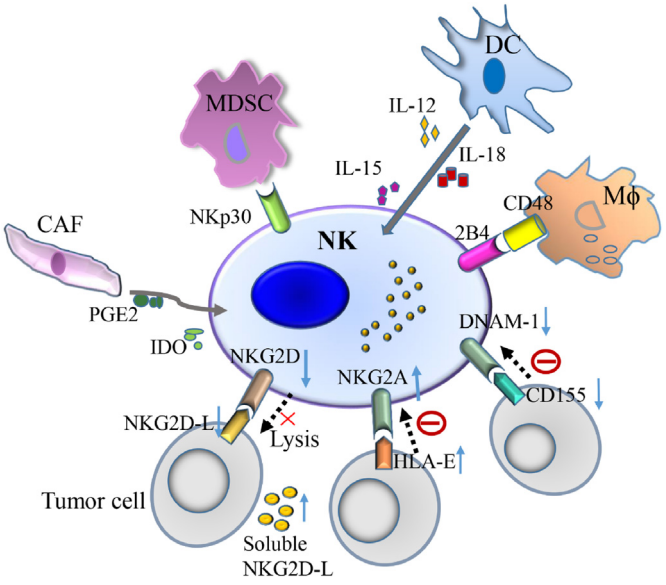

Fig. 1. Mechanisms of NK cell involvement in HCC tumour evasion.

factors inhibit the function of NK cells in the tumour microenvironment, and novel methodologies to effectively use these inhibitors to induce the activation of NK cells may be a future research direction to provide targets for the development of new tumour treatment strategies.

The activities of NK cells in HCC were suppressed via different mechanisms. NK cells in liver are exhausted because of the long exposure in chronic hepatitis and tumour cells. The percentage and number of NK cells decrease significantly, and cytotoxicity and cytokine secretion of cytokines is damaged. The balance of activity and inhibitory receptors is lost, and an imbalance characterized by decreased activity receptors (e.g., NKG2D, DNAM-1) and increased inhibitory receptors (e.g., NKG2A) emerges. Tumour cells downregulate the ligands of NK cell activating receptors (e.g., NKG2D-L, CD155), upregulate the ligands of NK cell inhibitory receptors (e.g., HLA-E), and release soluble NKG2D-L. Therefore, NK cells fail to recognize and bind tumour cells for killing and elimination. The cross-talk between immune cells in the tumour microenvironment may also affect NK cell activities. CAFs produce significant levels of immunosuppressive mediators, including PGE2, IDO, and TGF-β, which lead to the dysfunction of NK cells. MDSC-mediated inhibition to NK cell function is primarily dependent on the NK-activating receptor NKp30, which is one of the three natural cytotoxicity receptors responsible for the NK cell-mediated lysis of autologous immature dendritic cells. DCs assist in the function of NK cells via cell-to-cell contact and cytokine secretion (IFN-α/β, IL-12, IL-15 and IL-18), which contribute to the enhanced activation of NK cells and increased cytolysis of NK cells against HCC cells. Monocytes/Macrophage ($CD68^+$ cells) from HCC tissues strongly express CD48 proteins, and the dysfunction of NK cell induced by monocytes is markedly attenuated by blockade of CD48 receptor 2B4 on NK cells.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

The studies were supported by the grants from the National Natural Science Foundation of China (81303077), The Project of Medicine Science and Technology Development of Shandong (2017WS268), Natural Science Foundation of Shandong Province (ZR2018LH012) and Science and Technology Program Project of Shandong Academy of Medical Sciences (2018-15).

References

[1] A. Arzumanyan, H.M. Reis, M.A. Feitelson, Pathogenic mechanisms in HBV- and HCV-associated hepatocellular carcinoma, Nat. Rev. Cancer 13 (2013) 123–135.
[2] J.F. Perz, G.L. Armstrong, L.A. Farrington, Y.J. Hutin, B.P. Bell, The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide, J. Hepatol. 45 (2006) 529–538.
[3] S. Sengupta, N.D. Parikh, Biomarker development for hepatocellular carcinoma early detection: current and future perspectives, Hepatic oncology 4 (2017) 111–122.
[4] M. Sato, R. Tateishi, H. Yasunaga, H. Matsui, K. Fushimi, H. Ikeda, et al., Association between hospital volume and in-hospital mortality following radiofrequency ablation for hepatocellular carcinoma, BJS Open 1 (2017) 50–54.
[5] M.H. Attwa, S.A. El-Etreby, Guide for diagnosis and treatment of hepatocellular carcinoma, World J. Hepatol. 7 (2015) 1632–1651.
[6] Y. Liu, X. Cao, Immunosuppressive cells in tumor immune escape and metastasis, J. Mol. Med. 94 (2016) 509–522.
[7] A. Mandal, C. Viswanathan, Natural killer cells: in health and disease, Hematology/Oncology and Stem Cell Therapy 8 (2015) 47–55.
[8] A.M. Abel, C. Yang, M.S. Thakar, S. Malarkannan, Natural killer cells: development, maturation, and clinical utilization, Front. Immunol. 9 (2018) 1869.
[9] M.G. Morvan, L.L. Lanier, NK cells and cancer: you can teach innate cells new tricks, Nat. Rev. Cancer 16 (2016) 7–19.
[10] J.A. Hamerman, K. Ogasawara, L.L. Lanier, NK cells in innate immunity, Curr. Opin. Immunol. 17 (2005) 29–35.
[11] H. Peng, R. Sun, Liver-resident NK cells and their potential functions, Cell. Mol. Immunol. 14 (2017) 890–894.
[12] H. Spits, J.P. Di Santo, The expanding family of innate lymphoid cells: regulators and effectors of immunity and tissue remodeling, Nat. Immunol. 12 (2011) 21–27.
[13] S.D. Scoville, A.G. Freud, M.A. Caligiuri, Modeling human natural killer cell development in the era of innate lymphoid cells, Front. Immunol. 8 (2017) 360.
[14] C.I. Dahlberg, D. Sarhan, M. Chrobok, A.D. Duru, E. Alici, Natural killer cell-based therapies targeting Cancer: possible strategies to gain and sustain anti-tumor activity, Front. Immunol. 6 (2015) 605.
[15] Y. Zhang, B. Huang, The development and diversity of ILCs, NK cells and their relevance in health and diseases, Adv. Exp. Med. Biol. 1024 (2017) 225–244.
[16] M.A. Cooper, T.A. Fehniger, M.A. Caligiuri, The biology of human natural killer-cell subsets, Trends Immunol. 22 (2001) 633–640.
[17] A. Poli, T. Michel, M. Theresine, E. Andres, F. Hentges, J. Zimmer, CD56bright natural killer (NK) cells: an important NK cell subset, Immunology 126 (2009) 458–465.
[18] S.S. Farag, M.A. Caligiuri, Human natural killer cell development and biology, Blood Rev. 20 (2006) 123–137.
[19] M. Amand, G. Iserentant, A. Poli, M. Sleiman, V. Fievez, I.P. Sanchez, et al., Human CD56(dim)CD16(dim) cells as an individualized natural killer cell subset, Front. Immunol. 8 (2017) 699.
[20] B. Gao, W.I. Jeong, Z. Tian, Liver: an organ with predominant innate immunity, Hepatology 47 (2008) 729–736.
[21] D.G. Doherty, C. O'Farrelly, Innate and adaptive lymphoid cells in the human liver, Immunol. Rev. 174 (2000) 5–20.
[22] Z. Tian, Y. Chen, B. Gao, Natural killer cells in liver disease, Hepatology 57 (2013) 1654–1662.
[23] P.D. Krueger, M.G. Lassen, H. Qiao, Y.S. Hahn, Regulation of NK cell repertoire and function in the liver, Crit. Rev. Immunol. 31 (2011) 43–52.
[24] F.D. Shi, H.G. Ljunggren, A. La Cava, L. Van Kaer, Organ-specific features of natural killer cells, Nat. Rev. Immunol. 11 (2011) 658–671.
[25] H. Peng, Z. Tian, Re-examining the origin and function of liver-resident NK cells, Trends Immunol. 36 (2015) 293–299.
[26] K. Ishiyama, H. Ohdan, M. Ohira, H. Mitsuta, K. Arihiro, T. Asahara, Difference in cytotoxicity against hepatocellular carcinoma between liver and periphery natural killer cells in humans, Hepatology 43 (2006) 362–372.
[27] G. Jiao, B. Wang, NK cell subtypes as regulators of autoimmune liver disease, Gastroenterol. Res. Pract. 2016 (2016) 6903496.
[28] D. Vermijlen, D. Luo, C.J. Froelich, J.P. Medema, J.A. Kummer, E. Willems, et al., Hepatic natural killer cells exclusively kill splenic/blood natural killer-resistant tumor cells by the perforin/granzyme pathway, J. Leukoc. Biol. 72 (2002) 668–676.
[29] C.M. Sungur, W.J. Murphy, Positive and negative regulation by NK cells in cancer, Crit. Rev. Oncog. 19 (2014) 57–66.
[30] H.J. Pegram, D.M. Andrews, M.J. Smyth, P.K. Darcy, M.H. Kershaw, Activating and inhibitory receptors of natural killer cells, Immunol. Cell Biol. 89 (2011) 216–224.
[31] C. Chester, K. Fritsch, H.E. Kohrt, Natural killer cell immunomodulation: targeting activating, inhibitory, and co-stimulatory receptor signaling for Cancer immunotherapy, Front. Immunol. 6 (2015) 601.
[32] A.G. Freud, S. Zhao, S. Wei, G.M. Gitana, H.F. Molina-Kirsch, S.K. Atwater, et al., Expression of the activating receptor, NKp46 (CD335), in human natural killer and T-cell neoplasia, Am. J. Clin. Pathol. 140 (2013) 853–866.
[33] J. Schellekens, K. Gagne, S.G. Marsh, Natural killer cells and killer-cell immunoglobulin-like receptor polymorphisms: their role in hematopoietic stem cell transplantation, Methods Mol. Biol. 1109 (2014) 139–158.

[34] X. Xu, E. Narni-Mancinelli, C. Cantoni, Y. Li, S. Guia, L. Gauthier, et al., Structural insights into the inhibitory mechanism of an antibody against B7-H6, a stress-induced cellular ligand for the natural killer cell receptor NKp30, J. Mol. Biol. 428 (2016) 4457–4466.

[35] E. Alari-Pahissa, C. Grandclement, B. Jeevan-Raj, W. Held, Inhibitory receptor-mediated regulation of natural killer cells, Crit. Rev. Immunol. 34 (2014) 455–465.

[36] C. Sun, H. Sun, C. Zhang, Z. Tian, NK cell receptor imbalance and NK cell dysfunction in HBV infection and hepatocellular carcinoma, Cellular & Molecular Immunology 12 (2015) 292–302.

[37] M. Vitale, C. Cantoni, G. Pietra, M.C. Mingari, L. Moretta, Effect of tumor cells and tumor microenvironment on NK-cell function, Eur. J. Immunol. 44 (2014) 1582–1592.

[38] E. Viry, J. Baginska, G. Berchem, M.Z. Noman, S. Medves, S. Chouaib, et al., Autophagic degradation of GZMB/granzyme B: a new mechanism of hypoxic tumor cell escape from natural killer cell-mediated lysis, Autophagy 10 (2014) 173–175.

[39] A. Groth, S. Kloss, E.P. von Strandmann, U. Koehl, J. Koch, Mechanisms of tumor and viral immune escape from natural killer cell-mediated surveillance, Journal of Innate Immunity 3 (2011) 344–354.

[40] J. Bi, Z. Tian, NK Cell Exhaustion, Front. Immunol. 8 (2017) 760.

[41] L. Cai, Z. Zhang, L. Zhou, H. Wang, J. Fu, S. Zhang, et al., Functional impairment in circulating and intrahepatic NK cells and relative mechanism in hepatocellular carcinoma patients, Clin. Immunol. 129 (2008) 428–437.

[42] J. Gao, Z. Duan, L. Zhang, X. Huang, L. Long, J. Tu, et al., Failure recovery of circulating NKG2D(+)CD56(dim)NK cells in HBV-associated hepatocellular carcinoma after hepatectomy predicts early recurrence, Oncoimmunology 5 (2016) e1048061.

[43] E. Cariani, M. Pilli, V. Barili, E. Porro, E. Biasini, A. Olivani, et al., Natural killer cells phenotypic characterization as an outcome predictor of HCV-linked HCC after curative treatments, Oncoimmunology 5 (2016) e1154249.

[44] B. Fu, F. Wang, R. Sun, B. Ling, Z. Tian, H. Wei, CD11b and CD27 reflect distinct population and functional specialization in human natural killer cells, Immunology 133 (2011) 350–359.

[45] Q.F. Zhang, W.W. Yin, Y. Xia, Y.Y. Yi, Q.F. He, X. Wang, et al., Liver-infiltrating CD11b(−)CD27(−) NK subsets account for NK-cell dysfunction in patients with hepatocellular carcinoma and are associated with tumor progression, Cellular & Molecular Immunology 14 (2017) 819–829.

[46] M.D. Vesely, M.H. Kershaw, R.D. Schreiber, M.J. Smyth, Natural innate and adaptive immunity to cancer, Annu. Rev. Immunol. 29 (2011) 235–271.

[47] K. Karre, Natural killer cell recognition of missing self, Nat. Immunol. 9 (2008) 477–480.

[48] A. Zingoni, R. Molfetta, C. Fionda, A. Soriani, R. Paolini, M. Cippitelli, et al., NKG2D and its ligands: "one for all, all for one", Front. Immunol. 9 (2018) 476.

[49] R. Molfetta, L. Quatrini, A. Santoni, R. Paolini, Regulation of NKG2D-dependent NK cell functions: the Yin and the Yang of receptor endocytosis, Int. J. Mol. Sci. 18 (2017).

[50] R.A. Eagle, J. Trowsdale, Promiscuity and the single receptor: NKG2D, Nat. Rev. Immunol. 7 (2007) 737–744.

[51] L. Quatrini, R. Molfetta, B. Zitti, G. Peruzzi, C. Fionda, C. Capuano, et al., Ubiquitin-dependent endocytosis of NKG2D-DAP10 receptor complexes activates signaling and functions in human NK cells, Sci. Signal. 8 (2015) ra108.

[52] C.L. Sutherland, N.J. Chalupny, K. Schooley, T. VandenBos, M. Kubin, D. Cosman, UL16-binding proteins, novel MHC class I-related proteins, bind to NKG2D and activate multiple signaling pathways in primary NK cells, J. Immunol. 168 (2002) 671–679.

[53] E. Ullrich, J. Koch, A. Cerwenka, A. Steinle, New prospects on the NKG2D/NKG2DL system for oncology, Oncoimmunology 2 (2013) e26097.

[54] D.H. Raulet, S. Gasser, B.G. Gowen, W. Deng, H. Jung, Regulation of ligands for the NKG2D activating receptor, Annu. Rev. Immunol. 31 (2013) 413–441.

[55] L.L. Lanier, NKG2D receptor and its ligands in host defense, Cancer Immunology Research 3 (2015) 575–582.

[56] V. Jelencic, M. Lenartic, F.M. Wensveen, B. Polic, NKG2D: a versatile player in the immune system, Immunol. Lett. 189 (2017) 48–53.

[57] Mistry AR, O'Callaghan CA. Regulation of ligands for the activating receptor NKG2D. Immunology. 2007;121:439–47.

[58] S. Gasser, S. Orsulic, E.J. Brown, D.H. Raulet, The DNA damage pathway regulates innate immune system ligands of the NKG2D receptor, Nature 436 (2005) 1186–1190.

[59] M. Kloss, P. Decker, K.M. Baltz, T. Baessler, G. Jung, H.G. Rammensee, et al., Interaction of monocytes with NK cells upon toll-like receptor-induced expression of the NKG2D ligand MICA, J. Immunol. 181 (2008) 6711–6719.

[60] M. Jinushi, T. Takehara, T. Tatsumi, T. Kanto, V. Groh, T. Spies, et al., Expression and role of MICA and MICB in human hepatocellular carcinomas and their regulation by retinoic acid, Int. J. Cancer 104 (2003) 354–361.

[61] L. Fang, J. Gong, Y. Wang, R. Liu, Z. Li, Z. Wang, et al., MICA/B expression is inhibited by unfolded protein response and associated with poor prognosis in human hepatocellular carcinoma, Journal of Experimental & Clinical Cancer Research: CR 33 (2014) 76.

[62] K. Kohga, T. Tatsumi, T. Takehara, H. Tsunematsu, S. Shimizu, M. Yamamoto, et al., Expression of CD133 confers malignant potential by regulating metalloproteinases in human hepatocellular carcinoma, J. Hepatol. 52 (2010) 872–879.

[63] K. Kohga, T. Takehara, T. Tatsumi, H. Ishida, T. Miyagi, A. Hosui, et al., Sorafenib inhibits the shedding of major histocompatibility complex class I-related chain a on hepatocellular carcinoma cells by down-regulating a disintegrin and metalloproteinase 9, Hepatology 51 (2010) 1264–1273.

[64] H. Chen, W. Zhidan, R. Xia, W. Zhaoxia, J. Qing, G. Qiang, et al., Scorpion venom activates natural killer cells in hepatocellular carcinoma via the NKG2D-MICA pathway, Int. Immunopharmacol. 35 (2016) 307–314.

[65] S. Cheon, J.H. Lee, S. Park, S.I. Bang, W.J. Lee, D.Y. Yoon, et al., Overexpression of IL-32alpha increases natural killer cell-mediated killing through up-regulation of Fas and UL16-binding protein 2 (ULBP2) expression in human chronic myeloid leukemia cells, J. Biol. Chem. 286 (2011) 12049–12055.

[66] X. Mou, Y. Zhou, P. Jiang, T. Zhou, Q. Jiang, C. Xu, et al., The regulatory effect of UL-16 binding protein-3 expression on the cytotoxicity of NK cells in cancer patients, Sci. Rep. 4 (2014) 6138.

[67] H. Kamimura, S. Yamagiwa, A. Tsuchiya, M. Takamura, Y. Matsuda, S. Ohkoshi, et al., Reduced NKG2D ligand expression in hepatocellular carcinoma correlates with early recurrence, J. Hepatol. 56 (2012) 381–388.

[68] C. Sun, J. Xu, Q. Huang, M. Huang, H. Wen, C. Zhang, et al., High NKG2A expression contributes to NK cell exhaustion and predicts a poor prognosis of patients with liver cancer, Oncoimmunology 6 (2017) e1264562.

[69] K.W. Moore, R. de Waal Malefyt, R.L. Coffman, A. O'Garra, Interleukin-10 and the interleukin-10 receptor, Annu. Rev. Immunol. 19 (2001) 683–765.

[70] M.G. Lassen, J.R. Lukens, J.S. Dolina, M.G. Brown, Y.S. Hahn, Intrahepatic IL-10 maintains NKG2A+Ly49- liver NK cells in a functionally hyporesponsive state, J. Immunol. 184 (2010) 2693–2701.

[71] V.M. Braud, D.S. Allan, C.A. O'Callaghan, K. Soderstrom, A. D'Andrea, G.S. Ogg, et al., HLA-E binds to natural killer cell receptors CD94/NKG2A, B and C, Nature 391 (1998) 795–799.

[72] A.G. Brooks, F. Borrego, P.E. Posch, A. Patamawenu, C.J. Scorzelli, M. Ulbrecht, et al., Specific recognition of HLA-E, but not classical, HLA class I molecules by soluble CD94/NKG2A and NK cells, J. Immunol. 162 (1999) 305–313.

[73] P.F. Cheung, C.W. Yip, N.C. Wong, D.Y. Fong, L.W. Ng, A.M. Wan, et al., Granulin-epithelin precursor renders hepatocellular carcinoma cells resistant to natural killer cytotoxicity, Cancer Immunology Research 2 (2014) 1209–1219.

[74] P. Xiong, H.W. Sang, M. Zhu, Critical roles of co-activation receptor DNAX accessory molecule-1 in natural killer cell immunity, Immunology 146 (2015) 369–378.

[75] P. Qu, X. Huang, X. Zhou, Z. Lu, F. Liu, Z. Shi, et al., Loss of CD155 expression predicts poor prognosis in hepatocellular carcinoma, Histopathology 66 (2015) 706–714.

[76] J. Gong, L. Fang, R. Liu, Y. Wang, J. Xing, Y. Chen, et al., UPR decreases CD226 ligand CD155 expression and sensitivity to NK cell-mediated cytotoxicity in hepatoma cells, Eur. J. Immunol. 44 (2014) 3758–3767.

[77] Y. Ma, L.M. Hendershot, The role of the unfolded protein response in tumour development: friend or foe? Nat. Rev. Cancer 4 (2004) 966–977.

[78] V. Hernandez-Gea, S. Toffanin, S.L. Friedman, J.M. Llovet, Role of the microenvironment in the pathogenesis and treatment of hepatocellular carcinoma, Gastroenterology 144 (2013) 512–527.

[79] P.J. Murray, T.A. Wynn, Protective and pathogenic functions of macrophage subsets, Nat. Rev. Immunol. 11 (2011) 723–737.

[80] R. Noy, J.W. Pollard, Tumor-associated macrophages: from mechanisms to therapy, Immunity 41 (2014) 49–61.

[81] G. Solinas, G. Germano, A. Mantovani, P. Allavena, Tumor-associated macrophages (TAM) as major players of the cancer-related inflammation, J. Leukoc. Biol. 86 (2009) 1065–1073.

[82] Y. Liu, X. Cao, The origin and function of tumor-associated macrophages, Cellular & Molecular Immunology 12 (2015) 1–4.

[83] T. Krneta, A. Gillgrass, A.A. Ashkar, The influence of macrophages and the tumor microenvironment on natural killer cells, Curr. Mol. Med. 13 (2013) 68–79.

[84] Y. Wu, D.M. Kuang, W.D. Pan, Y.L. Wan, X.M. Lao, D. Wang, et al., Monocyte/macrophage-elicited natural killer cell dysfunction in hepatocellular carcinoma is mediated by CD48/2B4 interactions, Hepatology 57 (2013) 1107–1116.

[85] V. Umansky, C. Blattner, V. Fleming, X. Hu, C. Gebhardt, P. Altevogt, et al., Myeloid-derived suppressor cells and tumor escape from immune surveillance, Semin. Immunopathol. 39 (2017) 295–305.

[86] T.J. Stewart, M.J. Smyth, Improving cancer immunotherapy by targeting tumor-induced immune suppression, Cancer Metastasis Rev. 30 (2011) 125–140.

[87] P. Serafini, I. Borrello, V. Bronte, Myeloid suppressor cells in cancer: recruitment, phenotype, properties, and mechanisms of immune suppression, Semin. Cancer Biol. 16 (2006) 53–65.

[88] B. Hoechst, L.A. Ormandy, M. Ballmaier, F. Lehner, C. Kruger, M.P. Manns, et al., A new population of myeloid-derived suppressor cells in hepatocellular carcinoma patients induces CD4(+)CD25(+)Foxp3(+) T cells, Gastroenterology 135 (2008) 234–243.

[89] B. Hoechst, T. Voigtlaender, L. Ormandy, J. Gamrekelashvili, F. Zhao, H. Wedemeyer, et al., Myeloid derived suppressor cells inhibit natural killer cells in patients with hepatocellular carcinoma via the NKp30 receptor, Hepatology 50 (2009) 799–807.

[90] R. Kalluri, M. Zeisberg, Fibroblasts in cancer, Nat. Rev. Cancer 6 (2006) 392–401.

[91] A. Mazzocca, F. Dituri, L. Lupo, M. Quaranta, S. Antonaci, G. Giannelli, Tumor-secreted lysophostatidic acid accelerates hepatocellular carcinoma progression by promoting differentiation of peritumoral fibroblasts in myofibroblasts, Hepatology 54 (2011) 920–930.

[92] A. Orimo, P.B. Gupta, D.C. Sgroi, F. Arenzana-Seisdedos, T. Delaunay, R. Naeem, et al., Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion, Cell 121 (2005) 335–348.

[93] B. Erdogan, D.J. Webb, Cancer-associated fibroblasts modulate growth factor signaling and extracellular matrix remodeling to regulate tumor metastasis, Biochem. Soc. Trans. 45 (2017) 229–236.

[94] E.Y. Lau, J. Lo, B.Y. Cheng, M.K. Ma, J.M. Lee, J.K. Ng, et al., Cancer-associated fibroblasts regulate tumor-initiating cell plasticity in hepatocellular carcinoma through c-met/FRA1/HEY1 signaling, Cell Rep. 15 (2016) 1175–1189.
[95] M. Tahmasebi Birgani, V. Carloni, Tumor microenvironment, a paradigm in hepatocellular carcinoma progression and therapy, Int. J. Mol. Sci. 18 (2017).
[96] N. Kubo, K. Araki, H. Kuwano, K. Shirabe, Cancer-associated fibroblasts in hepatocellular carcinoma, World J. Gastroenterol. 22 (2016) 6841–6850.
[97] A.D. Barrow, M. Colonna, Tailoring natural killer cell immunotherapy to the tumour microenvironment, Semin. Immunol. 31 (2017) 30–36.
[98] T. Li, Y. Yang, X. Hua, G. Wang, W. Liu, C. Jia, et al., Hepatocellular carcinoma-associated fibroblasts trigger NK cell dysfunction via PGE2 and IDO, Cancer Lett. 318 (2012) 154–161.
[99] K. Miyazono, S. Ehata, D. Koinuma, Tumor-promoting functions of transforming growth factor-beta in progression of cancer, Ups. J. Med. Sci. 117 (2012) 143–152.
[100] K. Yamazaki, Y. Masugi, M. Sakamoto, Molecular pathogenesis of hepatocellular carcinoma: altering transforming growth factor-beta signaling in hepatocarcinogenesis, Dig. Dis. 29 (2011) 284–288.
[101] Q. Sui, J. Zhang, X. Sun, C. Zhang, Q. Han, Z. Tian, NK cells are the crucial antitumor mediators when STAT3-mediated immunosuppression is blocked in hepatocellular carcinoma, J. Immunol. 193 (2014) 2016–2023.
[102] R. Thomas, X. Yang, NK-DC crosstalk in immunity to microbial infection, J Immunol Res 2016 (2016) 6374379.
[103] M.A. Cooper, T.A. Fehniger, A. Fuchs, M. Colonna, M.A. Caligiuri, NK cell and DC interactions, Trends Immunol. 25 (2004) 47–52.
[104] M. Yamamoto, T. Tatsumi, T. Miyagi, H. Tsunematsu, H. Aketa, A. Hosui, et al., Alpha-fetoprotein impairs activation of natural killer cells by inhibiting the function of dendritic cells, Clin. Exp. Immunol. 165 (2011) 211–219.
[105] Z. Zhou, X. Yu, J. Zhang, Z. Tian, C. Zhang, TLR7/8 agonists promote NK-DC cross-talk to enhance NK cell anti-tumor effects in hepatocellular carcinoma, Cancer Lett. 369 (2015) 298–306.
[106] T.N. Nguyen-Pham, D.H. Yang, T.A. Nguyen, M.S. Lim, C.Y. Hong, M.H. Kim, et al., Optimal culture conditions for the generation of natural killer cell-induced dendritic cells for cancer immunotherapy, Cellular & Molecular Immunology 9 (2012) 45–53.
[107] K. Furumoto, S. Arii, S. Yamasaki, M. Mizumoto, A. Mori, N. Inoue, et al., Spleen-derived dendritic cells engineered to enhance interleukin-12 production elicit therapeutic antitumor immune responses, Int. J. Cancer 87 (2000) 665–672.
[108] P. Kalinski, R.B. Mailliard, A. Giermasz, H.J. Zeh, P. Basse, D.L. Bartlett, et al., Natural killer-dendritic cell cross-talk in cancer immunotherapy, Expert. Opin. Biol. Ther. 5 (2005) 1303–1315.
[109] M. Jinushi, T. Takehara, T. Tatsumi, N. Hiramatsu, R. Sakamori, S. Yamaguchi, et al., Impairment of natural killer cell and dendritic cell functions by the soluble form of MHC class I-related chain a in advanced human hepatocellular carcinomas, J. Hepatol. 43 (2005) 1013–1020.