Current perspectives on the immunosuppressive tumor microenvironment in hepatocellular carcinoma: challenges and opportunities

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A phase II clinical trial using tremelimumab included 21 patients with advanced HCC, with partial response rates and disease control rates of 17.6 and 76.4%, respectively [10]. PD-1 is expressed on B cells, T cells, natural killer (NK) cells, and dendritic cells (DCs) [11]. The PD-1 monoclonal antibody (mAb) blocks receptor binding of PD-L1 and PD-L2 to activate immune cells [12]. The researchers found that the PD-1 inhibitor nivolumab activates a sustained tumor-specific immune response and that side effects are controllable [13]. Treatment with PD-1 and CTLA-4 can stimulate T cell activation to enhance tumor eradication.

In the tumor microenvironment, non-malignant cells can help tumor cells to proliferate, invade and metastasize. The immunosuppressive features of tumor lesions participate not only as one of the major players inducing cancer progression but also a big challenge for effective immunotherapy. It has been found that immunosuppression associated with chronic inflammatory factors, such as growth factors, cytokines, and chemokines is generated by stroma and tumor cells [14, 15]. Multiple immune cells coexist and interact in a complex series of pathways that ultimately lead to tumor carcinogenesis. In the review, we will document some immunosuppressive cells, including tumor-associated macrophages (TAMs), marrow-derived suppressor cells (MDSCs), tumor-associated neutrophils (TANs), cancer-associated fibroblasts (CAFs) and regulatory T cells (Tregs) and their roles in cancer formation, which can lead to HCC.

**Tumor-associated macrophages**

TAMs inhibit anti-tumor immunity and promote tumor progression by expressing cytokines and chemokines. Preclinical studies have identified key pathways for TAMs recruitment, polarization and metabolism during tumor progression, and new therapies for these pathways can indirectly stimulate cytotoxic T-cell activation and recruitment [16–18]. Clinical trials of therapeutic agents currently promoting phagocytosis or inhibiting the survival, proliferation, transport or polarization of TAMs have shown improvement of cancer outcomes (Fig. 1).

TAMs are significant components of the microenvironment in HCC and associated with a poor prognosis of HCC patients. TAMs expression and density have been assessed by immunohistochemical staining from 253 HCC patients and results showed that CD68+ TAMs were not associated with clinicopathologic features and prognosis in HCC. However, low presence of CD86+ TAMs and high presence of CD206+ TAMs were significantly associated with invasive tumor phenotypes and with poorer overall survival (OS) as well as reduced time to recurrence [19]. TAMs develop from monocytes to functional macrophages and acquire various immunosuppressive functions at each stage of its differentiation to maintain the tumor microenvironment [20]. Repolarization of TAMs towards an antitumor phenotype was one approach to contributing to tumor regression [21]. Yang Y et al. first demonstrated that tumor cell-derived Wnt ligand stimulates M2 to transduce the polarization of TAMs via classical Wnt/β-catenin signaling, which results in immunosuppression in HCC [22]. Therefore, blocking Wnt secretion in tumor cells and/or activation of Wnt/β-catenin signaling in TAMs may be a potential strategy for future HCC treatment.

Previous literature has demonstrated that TAMs can produce a variety of chemokines, such as CCL17, CCL18...
and CCL22, which attract Tregs cells to cancer sites, thereby impeding cytotoxic T cell activation [23, 24]. This may lead to a positive feedback loop between TAMs and Tregs, providing a new dimension to the immunosuppressive effects of cancer. TAMs in HCC can also attract Tregs to regulate the tumor microenvironment. This phenomenon was found by Zhou J that the intratumoral distribution of Foxp3⁺ Tregs were associated with high density TAMs. The anti-interleukin-10 (IL-10) antibody partially blocked this increase, suggesting that TAMs may trigger an increase in the population of Foxp3⁺ Treg cells in the tumor, thereby promoting the progression of HCC [25]. Mechanistically, Wu Q et al. recently confirmed that TREM-1⁺ TAMs can respond to hypoxia and tumor metabolites via the ERK/NF-κβ pathway leading to accumulation of CCR6⁺ Foxp3⁺ Tregs [26]. This study highlights hypoxia-induced tumor immunosuppression by TREM-1⁺ TAMs that attracts CCR6⁺ Foxp3⁺ Tregs, and TREM-1⁺ TAMs confers HCC resistance to programmed cell death 1 ligand 1 (PD-L1) treatment.

TAMs are able to produce angiogenic factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor and transforming growth factor β. TAMs also induce angiogenesis by expressing matrix metalloproteinase (MMPs) [27–29]. Angiogenesis inhibition therapy has recently become a promising therapeutic strategy for HCC. Lipid-based nanoparticles (NP) targeting CXCR4 were developed to deliver VEGF siRNA specifically to HCC as an anti-angiogenic substance. The researchers demonstrated that AMD-modified NPs (AMD-NPs) can effectively transfer VEGF siRNAs into HCC and down-regulate VEGF expression in vitro and in vivo. Although SDF1α/CXCR4 axis is upregulation in hypoxia induction after anti-angiogenesis therapy, AMD-NPs combined with conventional sorafenib therapy or VEGF siRNA inhibition of CXCR4 can prevent the infiltration of TAMs [30]. However, there has been any association between TAMs and VEGF in HCC? One study has investigated the role of macrophages in HCC progression under sorafenib treatment and explored whether combination of drugs that deplete macrophages improved the antitumor effect of sorafenib. Results showed that although sorafenib significantly inhibited tumor growth and lung metastasis, it induced a significant increase in peripheral recruitment and intratumoral infiltration of F4/80- and CD11b-positive cells, which causes an increase of VEGF. Depletion of macrophages by clodronate or zoledronic acid (ZA) in combination with sorafenib significantly inhibited tumor progression, tumor angiogenesis, and lung metastasis [31]. These results indicate macrophages may have an important role in tumor progression under sorafenib treatment.

Preclinical studies have established that autophagy may play a role in the manipulation of TAMs function and tumor-related immunity. Chang CP et al. recently found that toll-like receptor 2 (TLR2)-associated ligands derived from HCC can stimulate the differentiation of M2 macrophages by selectively autophagy to control the homeostasis of NF-κβ RELA/p65 protein. TLR2 signaling induces NF-κβ RELA cytoplasmic ubiquitination and leads to degradation by SQSTM1/p62-mediated autophagy. Inhibition of autophagy will save NF-κβ activity and shape the phenotype of HCC polarized M2 macrophages [32]. The findings reveal a new role for autophagy in TAMs, which controls cellular function. Previous studies reported that Abies georgei’s natural product, named 747, is associated with xenophenol structure and exhibits sensitivity and selectivity as a CCR2 antagonist. In animals, 747 increases the number of CD8⁺ T cells in tumors by blocking tumor-infiltrating macrophage-mediated immunosuppression and inhibits in situ and subcutaneous tumor growth in a CD8⁺ T cell-dependent manner. In addition, 747 enhances the therapeutic effect of low-dose sorafenib without significant toxicity [33]. As shown in Table 1, treatment of TAMs targets in HCC has been documented and could be a new approach for treating HCC [34–38].

Marrow-derived suppressor cells

In cancer, the differentiation of myeloid cells often changes, producing a group of immature myeloid cells, which have strong immunosuppressive activity and impaired function as antigen-presenting cells (APCs) [39]. These cells are now known as MDSCs, a heterogeneous population of immature myeloid cell. MDSCs are also plastic and respond to microenvironment signals [40–42]. MDSCs can differentiate into macrophages, granulocytes and dendritic cells (DCs) in vitro. Therefore, MDSCs have significant diversity and plasticity, and are capable of changing their functional status in response to a variety of cytokines and growth factors in the tumor microenvironment. It has been reported that the immunosuppressive activity of MDSCs in the tumor microenvironment mainly includes (a) inducing differentiation and expansion of Tregs; (b) inhibiting the polarization of DCs, NKs and macrophages to the M2 phenotype; (c) depriving T cells of essential amino acids; (d) inducing oxidative stress (Fig. 2) [40–43]. We mainly reviewed the MDSCs in the tumor growth, angiogenesis, and metastasis of HCC in this context (Table 1) [44–52]. These evidence suggest that MDSCs contribute to the immunosuppressive network through multiple mechanisms and are potential immunotherapy targets for HCC.

MDSCs from HCC patients are unable to stimulate an allogeneic T-cell response, suppress T-cell proliferation, and have high arginase activity. Liu YT et al. used a hydrodynamic jet and transposon system to create a model that introduces a protein kinase and an open reading frames (ORFs) chromosomal encoding agent
| Molecule | Target cell | Therapeutic setting | Major effects | Reference |
|----------|-------------|---------------------|---------------|-----------|
| CCR2 TAMs | CCR2 antagonist | Inhibits recruitment of inflammatory monocytes, infiltration and M2-polarisation of TAMs | [34] |
| CCR2 TAMs | Anti-CCR2 | Promotes epithelial-to-mesenchymal transition by upregulating matrix metalloproteinase-2 | [35] |
| CCR2 TAMs | CCR2 monoclonal antibody | Inhibits recruitment of monocytes | [36] |
| CSF-1 TAMs | CSF-1 receptor antagonist | Reprograms polarization of TAMs | [37] |
| IL-6 TAMs | Anti-IL-6 | Blocks downstream effect of TAM products | [38] |
| IL-6 MDSCs | Anti-IL-6 | IL-6 expression levels strongly correlate with an MDSC phenotype and chemotherapy response in HCC patients | [44] |
| chemokine (C-C motif) ligand 26 MDSCs | Blockade of chemokine (C-C motif) ligand 26 | Knockdown of chemokine (C-C motif) ligand 26 in cancer cells profoundly reduces MDSC recruitment, angiogenesis, and tumor growth | [45] |
| SSAO MDSCs | SSAO inhibitors | May have an anti-tumor effect on HCC by inhibiting recruitment of CD11b+ and Gr-1+ cells and hindering angiogenesis | [46] |
| STAT3 MDSCs | Anti-STAT3 | Inhibiting STAT3 can enhance the clinical efficacy of CAR-T cells in LM through modulation of L-MDSC | [47] |
| CCRK MDSCs | Anti-CCRK | Hepatic CCRK induction in transgenic mice stimulates mTORC1-dependent G-csf expression to enhance polymorphonuclear MDSCs recruitment and tumorigenicity in HCC | [48] |
| CCL9/CCR1 MDSCs | Blockade of CCL9/CCR1 | CCL9 secreted by splenic macrophages induces a CCR1-dependent accumulation of MDSCs in the spleen in a murine H22 hepatoma model | [49] |
| ENTPD2/CD39L1 MDSCs | Blockade of ENTPD2/CD39L1 | Hypoxia induces the expression of ENTPD2 on cancer cells leading to elevated extracellular S'-AMP, which promotes the maintenance of MDSCs by preventing their differentiation in HCC | [50] |
| PD-L1 MDSCs | PD-1 monoclonal antibody | PD-L1+ MDSCs could be used as a new biomarker of HCC | [51] |
| IL-18/TLR2 MDSCs | Blockade of IL-18/TLR2 | IL-18 administration was sufficient to induce accumulation of MDSC, whereas hepatocyte-specific silencing of IL-18 in TLR2(-/-) mice decreased the proportion of MDSC | [52] |
| TGF-β/Axl/CXCL5 TANs | Blockade of TGF-β/Axl/CXCL5 | The synergy of TGF-β and Axl induces CXCL5 secretion, causing the infiltration of neutrophils into HCC tissue. | [72] |
| cortisol TANs | Inhibition of cortisol | increased cortisol production and TAN/TAM infiltration as primary factors in the gender disparity of HCC development in both fish and human | [73] |
| CXCR2/CXCL1 TANs | Blockade of CXCR2/CXCL1 | The CXCR2-CXCL1 axis can regulate neutrophil infiltration into HCC tumor tissues and might represent a useful target for anti-HCC therapies | [74] |
| CXCL17 TANs | Anti-CXCL17 | CXCL17 expression was associated with more CD68 and less CD4 cell infiltration | [75] |
| CXCR6 TANs | Anti-CXCR6 | Human HCC samples expressing high levels of CXCR6 contained an increased number of CD68+ neutrophils and microvesicles | [76] |
| miRNA-21 CAFs | MiRNA-21 inhibitor | High level of serum exosomal miRNA-21 was correlated with greater activation of CAFs and higher vessel density in HCC patients | [84] |
| CD24 CAFs | Anti-CD24 | HGF and IL6 secreted by CAFs promoted the stemness properties of CD24+ HCC cells through the phosphorylation of STAT3 | [85] |
| LOXL2 CAFs | Anti-LOXL2 | The secreted LOXL2 promotes fibronectin production, MMP9 and CXCL12 expression and BMDCs recruitment to assist pre-metastatic niche formation | [86] |
| PD-L1/IL6/STAT3 CAFs | Blockade of PD-L1/IL6/STAT3 | HCC-CAF s regulate the survival, activation, and function of neutrophils within HCC through an IL6-STAT3-PDL1 signaling cascade | [87] |
| IL6/STAT3 CAFs | blockade of IL6/STAT3 | IL-6 secreted by CAFs promotes stem cell-like properties in HCC cells by enhancing STAT3/Notch signaling | [88] |
for tumor antigens. The transposon-based Akt/N-Ras-induced HCC mouse model allows researchers to monitor tumor growth non-invasively, quantify and characterize endogenous or over-transferred CD8+ T cell responses [53]. These characteristics make it a convenient preclinical model for the evaluation of immunological checkpoint inhibitors and cellular immunotherapy HCC. MDSCs was found to cause inhibition of CD8+ T-cell responses. In addition, recent studies have reported that inhibition of tumor CCRK or liver IL-6 increases interferon γ+ tumor necrosis factor-α+CD8+ T-cell infiltration and impaired tumorigenicity and is restored by recovery of MDSCs. It is worth noting that the tumor CCRK depletion up-regulated the expression of PD-L1 and increased the expression of intratumoral CD8+ T cells, thereby enhancing the effect of PD-L1 blocking HCC [54].

Additionally, these MDSCs cocultured with autologous T cells induce Treg expansion, which mitigates effector T-cell function. Kalathil S et al. recorded an increase in the number of Tregs, MDSC, PD-1+-exhausted T cells,
and an increase in immunosuppressive cytokine levels in HCC patients, revealing the potential mechanistic network for immune disorders in HCC patients compared with the normal control group [55]. Other mechanisms have been described, in which MDSCs affect T-cell function, survival, and trafficking. Similar to TAMs, MDSCs express galectin-9 that binds to TIM-3 on T cells, inducing T-cell apoptosis [56]. MDSCs can also impair natural killer (NK) cell function. In HCC, MDSCs inhibit NK cell cytotoxicity and cytokine release, which is mediated by the NKp30 receptor [57]. Regarding the interaction between MDSCs and DC cells, it has been reported that MDSC inhibits TLR-ligand-induced IL-12 by IL-10 production and inhibits T-cell stimulating activity of DCs in HCC [58].

Because of the tumor-promoting and immunosuppressive effects of bone marrow cells, it is of great interest to target them to enhance the efficacy of conventional cancer therapies. The recently approved chemotherapeutic agent, trabectedin, not only targets tumor cells, but induces rapid apoptosis of bone marrow cells [59]. Clinical trials have shown that trabectedin also has a strong cytotoxic effect on liver cancer cells [60]. Therefore, trabectedin may be a potential treatment for HCC. Another potential target is estrogen, which inhibits myeloid cell function in HCC [61]. Estrogen inhibits IL-6 exposure to macrophages exposed to necrotic hepatocytes and reduces the risk of liver cancer in DEN-treated female mice [62]. Estrogen inhibits tumor necrotic cell-STAT6 activation by inhibiting Janus kinase, resulting in a reduced HCC model in mice [63]. Thus, estrogen therapy may help disrupt the development and function of HCC bone marrow cells. Therefore, targeting bone marrow cells represents a point of further research as a possible adjuvant therapy to attenuate HCC progression.

**Tumor-associated neutrophils**

It is clear that bone marrow-derived cells, including TAMs, TANs, and MDSCs, promote tumor progression [64–66]. In recent years, many studies have shown that TANs not only promote tumor growth, but also anti-tumor effects on tumors, and can regulate their different phenotypes through tumor signal transduction. TANs can be divided into two major subtypes, N1 (anti-tumor) and N2 (pro-tumor) and the plasticity of these subtypes depends on the presence of TGF-β [67, 68]. Neutrophils can polarize TGF-β to the N2 phenotype while TGF-β together with increased inhibition of IFN-β induces N1 phenotype [69].

Depending on the microenvironment of the tumor, TANs can promote or inhibit tumor progression by releasing cytokines. Zhou SL and his colleagues found that CCL2 and CCL17 are the most highly expressed cytokines in peripheral blood neutrophils (PBNs) activated by TANs and HCC cells. The number of CCL2+ or CCL17+ TANs is related to tumor size, microvascular infiltration, tumor embedding, tumor differentiation and staging. Compared to PBN-conditioned medium, TAN-conditioned media and recombinant CCL2 and CCL17 increased the migration activity of HCC cells or mouse macrophages and Tregs [70]. Taken together, this evidence suggests that TANs recruit macrophages and Treg cells into HCCs to promote their growth, progression, and resistance to sorafenib. Surprisingly, the same team reported that the secretion secreted BMP2 and TGF-β2 and
triggered the expression of miR-301b-3p in HCC cells, followed by inhibition of the limbal gene expression membrane protein (LSAMP) and CYLD Lysine deubiquitinase and increased stem cell characteristics in HCC cells. These TAN-induced hepatoma stem cell-like cells are active in NF-κB signaling, a higher level of secretion of C-X-C-chemokine 5 (CXCL5) and recruitment of more TANs infiltration, suggesting a positive feedback loop [71]. Additionally, we have literature some important molecules which might target TANs in HCC (Table 1) [72–76].

Cancer-associated fibroblasts
Recent studies have shown that communication between cancer cells and fibroblasts is very important, and these fibroblasts are called CAFs [77, 78]. CAFs promote the proliferation, invasion and metastasis of tumors by secreting various growth factors and cytokines [79, 80]. In HCC, Mano Y et al. established that primary CAFs and non-cancerous liver fibroblasts from 15 patients undergoing HCC resection. They found that endogenous and exogenous BMP4 activate hepatic fibroblasts to gain the ability to secrete cytokines and enhance the invasiveness of cancer cells. BMP4 is one of the regulators of CAFs function in the HCC microenvironment [81].

CAFs train NK cells to obtain an inactive phenotype and produce an unresponsive state in the tumor. Li T et al. found that HCC-derived fibroblasts induced NK cell dysfunction significantly better than foreskin-derived fibroblasts, which were characterized by low expression of cytotoxic molecules and cell surface markers, and impaired production of cytokines. They also noted that PGE2 and IDO from activated fibroblasts inhibit the activation of NK cells, thereby creating favorable conditions for tumor progression [82]. In addition, CAF can recruit regulatory DCs
through IL-6-mediated STAT3 activation and educate them to obtain a tolerogenic phenotype and up-regulate Treg production by secreting TGF-β in the tumor microenvironment [83]. In summary, CAFs play an important role in the development and progression of cancer cells and targeting CAFs may be effective in treating fibrosis and preventing HCC progression (Tables 1, [84–90].

Anticancer therapies targeting CAFs or cytokine inhibitors secreted by CAFs have recently been actively studied. Inhibitors of TGF-beta signaling have been shown to block HCC growth and progression by modulating EMT in different experimental models [91]. Several studies have explored the active targeting of CAFs to provide therapeutic compounds. A recent report presented anti-fibrotic drugs such as PRI-724, conophylline, follistatin, salvianolic acid, Gliotoxin, Curcumin, sulfasalazine, and tanshinone I, which inhibit activated HSC and/or induce apoptosis [92–96]. It is believed that these drugs can not only control fibrosis, but also inhibit HCC by controlling the function of CAFs. It has been reported that fibroblast growth factor receptor 1 is overexpressed in the fiber layer HCC [97]. CAFs stimulate tumor cells through FGF and produces fibrosis [98, 99]. Treatments that target CAFs may be effective in fibrolamellar HCC. CAFs are one of the most important components in the tumor microenvironment and promote cancer cell growth and invasion through various mechanisms. CAFs are important for the initiation and progression of cancer cells and for the treatment of CAFs to effectively treat fibrosis and prevent HCC progression.

**Table 2** Clinical trials in HCC using immune checkpoint inhibitors

| Antibody features | Antibody name     | NCT number                                      | Status     |
|-------------------|-------------------|-------------------------------------------------|------------|
| anti-CTLA4        | Ipilimumab        | NCT03682276,NCT03510871,NCT03222076,NCT03203304 | Ongoing    |
| anti-CTLA4        | Tremelimumab      | NCT01853618,NCT02519348,NCT02519348,NCT03298451, NCT02821754,NCT03482102, NCT03638141 | Ongoing    |
| anti-PD-1         | Nivolumab         | NCT01658878,NCT025275609,NCT03383458,NCT03682276, NCT03071094,NCT03382886,NCT03781960,NCT03033446, NCT03510871,NCT03299946,NCT03059147,NCT03630640, NCT03418922,NCT03655613,NCT02837029,NCT03785210,NCT03695250,NCT03655002,NCT02859324,NCT03439891 | Ongoing    |
| anti-PD-1         | Pembrolizumab     | NCT02702401,NCT03062358,NCT03713593,NCT02658019, NCT03753659,NCT03006926,NCT03519997,NCT03337841, NCT03163992,NCT03397654,NCT03316872,NCT03099564,NCT02940496,NCT03419481,NCT03647163,NCT02309507,NCT03211416,NCT03347292,NCT03511222,NCT03095781, NCT03259867,NCT02559866,NCT02432963 | Ongoing    |
| anti-PD-1         | Tislelizumab      | NCT03419897,NCT03412773                         | Ongoing    |
| anti-PD-1         | Spartalizumab     | NCT02989840,NCT02795429,NCT02947165,NCT02325739 | Ongoing    |
| anti-PD-1         | Camrelizumab      | NCT02989922,NCT03463876,NCT02942329,NCT03722875, NCT03605706,NCT03793725,NCT03764293,NCT03601598 | Ongoing    |
| anti-PD-L1        | Durvalumab        | NCT03298451,NCT03778957,NCT03482102,NCT02519348, NCT03638141,NCT03257761,NCT02821754,NCT02572687, NCT03539822 | Ongoing    |
| anti-PD-L1        | Avelumab          | NCT03380126, NCT03289533                         | Ongoing    |
| anti-PD-L1        | Atezolizumab      | NCT03170960, NCT03755791, NCT03434379            | Ongoing    |

**Tumor-infiltrating Tregs**

Tregs cells are the subset of CD4+ T cells and identified with the CD25 marker. CD4+ CD25+ compartment of cells is approximately 1–2% of peripheral CD4+ cells. Tregs cells do not only limit autoimmune responses, they also dampen responses against microbial and viral antigens, allergens, tumors, and allografts. Tumor-associated Tregs directly promote tumor evasion by a number of contact-dependent and contact-independent mechanisms [100, 101].

The number of Tregs has been reported to increase in patients with HCC [102]. Yang et al. found that the proportion and absolute number of CD4+CD25+ T cells in the surrounding area of the tumor were significantly increased [103]. The other group showed a higher frequency of Tregs in peripheral blood from HCC patients compared to HCV patients and healthy subjects. Mechanistically, Huh7 culture supernatants appear to promote CD4+CD25+ T-cell proliferation and inhibit CD4+CD25+ T-cell proliferation [104]. In addition, the frequency of circulating Tregs was linked to the disease progression and had a potential of serving as a significant biomarker in HCC patients [105, 106]. Sorafenib is a multikinase inhibitor that could reduce the frequency of hepatic infiltrating Tregs by suppressing TGF-β signaling [107]. As a result, these evidence indicates
suppressing Tregs might be one of the significant targets for the induction of an immune response for HCC.

CTLA-4 is member of immunoglobulin superfamily homologous to CD28 with higher affinity for B7. CTLA-4 inhibits early T cell immune response, mainly in lymphoid tissues [108]. In naive T cells, CTLA-4 localized in the intracellular space and expressed on the cell surface upon stimulatory signals. Whereas in Tregs, CTLA-4 is constitutively expressed and is involved in Treg suppressive functions [109]. Several studies investigated PD-1 and PD-L1 expression in the context of HCC and found that PD-L1 expression was localized mainly in neoplastic or intratumoral inflammatory cells [110, 111]. Moreover, PD-1/ PD-L1 interaction was demonstrated to contribute to immune suppression in HCC [112]. High level of PD-L1 expression was shown in tumors with a high number of tumor infiltrating lymphocytes (TILs) and shorter overall survival [113]. There are several clinical trials investigating the efficacy of monoclonal antibodies (mAb) against CTLA-4 and PD-1/PD-L1 as single agent treatment. In this review, we have extensively studied the efficacy of the current proposed immunotherapy for Tregs in patients with HCC. (Fig. 3) (Tables 1,2) [114–127].

Conclusion and perspectives

Due to high mortality, limited treatment and poor prognosis of HCC, new immunotherapy treatments are urgently needed. For example, blocking the activation of immunosuppressive receptors on T-cells has become a new focus of therapy. Immunosuppressive cells, including TAMs, MDSCs, TANs, CAFs, and Tregs are key components of the tumor microenvironment that promote HCC growth and invasion. There is an interaction between these types of immune cells leading to tumor immune escape. These cells often have both anti-cancer and cancer-promoting effects, and their specific regulation and mechanism of action are not well understood. The differentiation, maturation and function of immune cells require the participation and regulation of cytokines and chemical factors, as well as the interaction of receptors and related ligands. These factors create a tumour microenvironment that inhibits the anti-tumor activity of immune cells, promoting the occurrence of HCC. Further research involving paired tumor biopsy will inform immunotherapy treatments and improve the prognosis of patients with HCC. In addition, advances in DNA and RNA sequencing technologies provide insights into the mechanisms of HCC progression to identify other targets. Altogether, these approaches to treatment brings new hope to HCC patients.

Abbreviations

AMD-NPs: AMD-modified NPs; APCs: Antigen-Presenting Cells; CAFs: Cancer-associated fibroblasts; CSF: Colony stimulating factor-1 receptor; CTLA-4: Cytotoxic T lymphocyte-associated protein 4; CXCL5: CX-C-chemokine 5; DCs: Dendritic Cells; HCC: Hepatocellular carcinoma; IL-10: Interleukin-10; LSAMP: Limbal gene expression membrane protein; mAb: Monoclonal antibodies; MDSCs: Marrow-derived suppressor cells; MMPs: Matrix metalloproteinase; NK: Natural killer; NP: Nanoparticles; ORFs: Open Reading Frames; PBNs: Peripheral blood neutrophils; PD-1: Programmed cell death protein 1; PD-L1: Programmed cell death ligand 1; TAMs: Tumor-associated macrophages; TANs: Tumor-associated neutrophils; TILs: Tumor infiltrating lymphocytes; TLR2: Toll-like Receptor 2; Tregs: Regulatory T cells; VEGF: Vascular Endothelial Growth Factor; ZA: Zoledronic Acid

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Authors’ contributions

There are 3 first authors in this manuscript and they have equally contributed to this project. Dr. CL, DR and BZ was responsible for gathering information of the related research and designing the review. Dr. WZ was responsible for drawing the pictures. Furthermore, we have three corresponding authors in this manuscript. Dr. WT has contributed to information interpretation, editing and critical revision of the manuscript. Dr. XW and ZC have contributed to study design and critical revision of the manuscript. Dr. WT, ZC, and XW were also responsible for handling the revisions and resubmission of revised manuscripts. All authors read and approved the final manuscript.

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