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Review Article

Heterogeneity of monocytes in cancer

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Abstract: Monocytes, a crucial element of the innate immune system, act as the primary cells in the body's immune response. Approved by the International Federation for Immunology in 2010, monocytes are categorized into three subsets based on the degree of cell surface molecule expression: classical monocytes, intermediate monocytes, and non-classical monocytes. Generally, different monocyte subsets have diverse responsibilities and can mutually transform to maintain the stability of the internal environment. Distinctions in functional characteristics and associations with diseases have been identified among the various monocyte subsets. This review aims to describe the expression and functions of monocytes in detail and discuss their roles in cancer immunity, which offers a novel approach for the diagnosis, treatment, and prognosis of tumors by exploring and summarizing the distribution of monocyte subsets in tumors. By delving into the distribution and functional characteristics of different monocyte subsets in tumors, it holds the promise of guiding individualized therapies and more precise tumor management.

Keywords: Monocytes, cancers, immune responses, prognosis

Introduction

Monocytes are critical defense components that play an important role in the primary innate immune response [1]. After birth, monocytes derive from haematological precursors in the bone marrow and enter the blood circulation, from which they are recruited into tissues throughout the body [2]. Over recent years these cells have been characterized in detail with the use of cell surface markers and flow cytometry, and subpopulations have been described. Subset identification of monocytes is based on the relative expression of CD14 [co-receptor for toll-like receptor 4 (TLR4) and mediates lipopolysaccharide (LPS) signaling] and CD16 (Fc gamma receptor IIIa) [3]. The classical monocytes show high CD14 expression but no CD16 ($CD14^{++}CD16^{-}$), the intermediate monocytes show a high level of CD14 together with low CD16 ($CD14^{++}CD16^{+}$), and the non-classical monocytes express a low level of CD14 together with high CD16 ($CD14^{+}CD16^{++}$). When the intermediate and the non-classical monocytes are not separately defined, then we propose to address them collectively as $CD16^{+}$ monocytes [1]. Murine monocytes are evenly distributed by their relative expression of the Ly6C antigen and are, for the most part, functionally distinct. $Ly6C^{high}$ monocytes co-express CCR2 and CD62L with low expression of the fractalkine receptor CX3CR1, whereas $Ly6C^{low}$ monocytes have elevated expression of CX3CR1 with lower expression of CCR2 [4, 5]. This expression pattern supports the present view that $Ly6C^{high}$ monocytes are closely related to human classical ($CD14^{++}CD16^{-}$) monocytes and conversely, $Ly6C^{low}$ monocytes are analogous to the non-classical $CD14^{+}CD16^{++}$ population [6].

During both homeostasis and pathological conditions, each subpopulation may assume distinct roles. The heterogeneity of these subpopulations enhances our understanding of inflammation pathogenesis, and an increased

proportion of a specific population could potentially serve as a biomarker for disease [7]. Classical monocytes not only engage in the process of tissue repair and immune response but also possess the capabilities of phagocytosis, facilitating wound healing, and resisting apoptosis [3]. Meanwhile, they can also promote inflammatory responses, which are mainly dependent on their ability to express pro-inflammatory S-100 proteins, eg S100A12 and S100A8/9 [8]. The intermediate monocytes are responsible for the proliferation and stimulation of T cells. They express higher levels of surface markers involved in antigen-presenting cell-T cell interactions [3]. Genes associated with cytoskeleton mobility are mostly expressed by the non-classical subset. Signs of inflammation or damage mobilize them to rapid transmigration [9]. Their genes also define complement components, negative regulation of transcription, and proapoptosis abilities [7].

The investigation of monocyte heterogeneity has emerged as a pivotal area in cancer biology and clinical oncology, with its significance spanning the entire research continuum from basic mechanistic exploration to clinical translational application. Monocyte heterogeneity exerts multifaceted impacts on cancer diagnosis, treatment, and prognostic assessment. In the context of diagnosis, it provides a refined molecular subtyping tool for tumors [10]. Regarding therapeutic interventions, it elucidates the differential mechanisms underlying responses to targeted agents and immunotherapy [11]. For prognostic evaluation, it enhances the accuracy of risk stratification models [12]. This heterogeneity is exemplified by the distinct subsets described across various cancers, the key features of which are compiled for comparison in **Table 1**.

Origin and development of monocytes

Monocytes in circulation are derived from hematopoietic stem cells (HSCs), which give rise to monocytes in a step-wise manner via common myeloid progenitors (CMPs), granulocyte-monocyte progenitors (GMPs), monocyte-dendritic cell progenitors (MDPs), and common monocyte progenitors (cMoPs) [13, 14]. The classical model of hematopoiesis proposes that MDPs arise from GMPs and give rise to monocytes through a cMoP stage [15]. In a recent study, Yanez et al. showed that MDPs arose directly from CMPs independently of GMPs and that GMPs and MDPs gave rise to monocytes via MPs and cMoPs, respectively, although no phenotypic difference between MPs and cMoPs was reported [16].

Transcription factors play crucial roles in the differentiation and development of distinct subsets of monocytes. IRF 8 mainly acts as an activator during monocyte differentiation, binds to the promoter-distal region, and promotes the histone modification properties of the enhancer. Targeting IRF8 enhancers, such as the RUNx-CBFβ complex, can expand protective monocytes for infection or tumor immunotherapy [17]. Kruppel-like factor 4 (KLF4) was identified as mediated indirect IRF8 key transcription factors of the target genes of inducing, which is also necessary for $Ly6C^+$ mononuclear cells [18]. As the most important transcription factor in monocyte development, PU.1 is highly expressed and cooperates with myeloid transcription factors to drive tissue-specific macrophage transcriptional programs [19]. Bioinformatic analyses show that PU.1 is a predicted upstream transcription factor of mammalian ZBTB14, a Zbtb14-PU.1 negative feedback loop might regulate monocyte and macrophage development [20]. The CSF-1 growth factor is essential for monocyte development, as it not only extends the survival of CMPs but also enhances their proliferation and division, ultimately directing their differentiation toward monocyte formation [21].

Distribution characteristics and phenotypic changes of monocyte subsets in cancers

Monocyte subsets and head and neck cancer

The proportion of intermediate monocytes was lower in patients with squamous cell carcinoma of the head and neck (SCCHN), however, there was a significant increase in the expression of HLA-G, PD-L1, and CD51 molecules, while the levels of mature markers CX3CR1 and CD68 were decreased [22]. The findings indicated that SCCHN patients exhibited a low abundance and immature state of intermediate monocytes, which may be indicative of an unfavorable clinical prognosis. Latest study reports that Bestrophin1 (BEST1), a component protein of $Ca2^+$-activated Cl^- channels (CaCCs), is highly expressed on classical monocytes in the peripheral blood of HNSCC patients. The BEST1 upregulated subset originates from the tumor microenvironment and is induced by tumor cytokines, accelerating tumor progression by

Table 1. Category and feature of monocytes in cancers

Tumor type	Author, year	Monocyte subsets	Clinical characteristic	Refs
Squamous cell carcinoma of the head and neck (SCCHN)	Sakakura K et al., 2021	Intermediate monocytes	Lower in patients; Unfavorable clinical prognosis	[22]
	Zhang L et al., 2023	Classical monocytes	Bestrophin1 (BEST1) is highly expressed	[23]
Breast cancer	Gao ZJ et al., 2024	$CD14^+CD16^+$ monocyte	Increased in patients	[26]
	McGinnis CS et al., 2024	$CD14^+CD16^+$ monocyte	Negatively associated with tumour size and staging	[28]
	Speigl L et al., 2018	$CD14^+HLA\text{-}DR^-$ cells	At higher levels; Exhibit potent suppressive effects on autologous T cell proliferation	[29]
	Massa C et al., 2020	Classical, non-classical, and intermediate monocytes	Treatment with nanoparticle albumin-bound paclitaxel for 12 weeks resulted in a significant reduction in the numbers	[34]
	Kyrgidis A et al., 2017	$CD14^+CD23^+$, $CD14^+CD23^-$, and $CD14^+CD123^-$ monocytes	An increase	[36]
Non-small cell lung cancer (NSCLC)	KwiecieŃ I et al., 2020	Classical and intermediate monocytes	Increased	[38]
	Wang L et al., 2023	$CD14^+$ monocytes	Revealed a dysfunctional phenotype; lower HLA-DR expression and reduced granzyme B, and proinflammatory cytokines	[40]
	Xue R et al., 2021	$CD16^+$ monocytes	Exhibited elevated levels of Tie2 expression; compromised pulmonary function and diminished survival rates	[42]
Lung squamous carcinomas (LUSC) Lung adenocarcinoma	Porrello A et al., 2018	Inflammatory monocytes ($CCR2^{High}CD14^+CD16^{Low}$)	Exhibited heightened levels of factor XIIIA; unfavorable survival outcomes	[43]
	Desharnais L et al., 2025	Classical monocytes	High	[44]
	Rivas-Fuentes S et al., 2018	Classical and intermediate $HLA\text{-}DR^+$ monocytes	Decreased	[46]
Colorectal cancer (CRC)	Krijgsman D et al., 2020	The overall proportion of monocytes	A positive correlation with TNM staging, tumor differentiation degree	[47]
	Wang F et al., 2023	$CD14^+$ monocytes	the most enriched subpopulation in the peripheral blood	[48]
	Li C et al., 2015	$CD14^+CD169^+$ monocytes	Associated with disease stage and positively correlated with serum levels of IL-10 and CEA	[49]
	Väyrynen JP et al., 2021	$CD14^+HLA\text{-}DR^+$ cells	Associated with prolonged survival	[53]
Hepatocellular carcinoma (HCC)	Myojin Y et al., 2025	Classical monocytes ($CD14^{++}CD16^-$)	Significantly increased	[59]
	Liu LZ et al., 2019	$CCR1^+CD14^+$ monocytes	Inhibited anti-tumor immune responses, facilitated angiogenesis, and expedited tumor invasion and metastasis	[61]
	Tu X et al., 2024	$S100A9^+CD14^+$ monocytes	Promote tumor immune escape	[62]
	Yasuoka H et al., 2020	$PD\text{-}L1^+$ $PD\text{-}L2^+$ $CD14^+$ cells	Exhibited a more unfavorable prognosis	[65]
	Chang JQ et al., 2025	$CD14^+HLA\text{-}DR^-/low$ cells	Contribute to $CD8^+$T cell exhaustion	[66]
Melanoma	Chavan et al., 2014	$CD14^+CD16^-$ classical monocytes	Decreased	[71]
	Funck F et al., 2020	slan+ (6-sulfo LacNAc) non-classical monocytes	Elevated	[72]
	Krieg C et al., 2018	$CD14^+CD16^-HLA\text{-}DR^{high}$ monocytes	Served as the strongest independent predictor of PFS and OS	[74]
	Kim J et al., 2024	$CD244^-$ monocytes	Associated with improved survival rates	[75]

Ovarian cancer	Prat M et al., 2020	Intermediate monocytes	Increased; Associated with a reduction in effector T cell content and the presence of soluble immunosuppressive mediators	[81]
	Wang X et al., 2017	Tie2 expressing monocytes (TEM)	Increased; promoted angiogenesis through IGF1 signaling pathway both in vivo and in vitro experimental models	[82]
	Stenzel A E et al., 2021	$CD14^{+}HLA\text{-}DR^{-}$ monocytes	Increased	[83]
Oral squamous cell carcinoma	Song Y et al., 2018	$CD14^{+}CD16^{+}$ intermediate monocytes	Higher	[84]
		$CD14^{+}CD16^{-}$ classical monocytes	Decreased	
Pancreatic cancer	Baj-Krzyworzeka M et al., 2010	$CD14^{+}CD16^{++}$ cells	The predominant subset of monocytes involved in anti-tumor response	[86]
	Javeed N et al., 2017	$CD14^{+}HLA\text{-}DR^{-}$ monocytes	Increased	[89]
	Caronni N et al., 2023	Circulating monocytes	Protein levels of IL-1β increased substantially upon recruitment to tumors	[90]
B-ALL	Witkowski MT et al., 2020	$CD14^{+}CD16^{++}$ non-classical monocytes	A significant increase	[91]
		$CD14^{++}CD16^{-}$ classical monocytes	A significant reduction	
Diffuse large B-cell lymphoma (DLBCL)	Le Gallou S et al., 2021	Classical and intermediate monocytes	Accumulated; exhibited an inflammatory phenotype	[92]
		Non-classical monocytes	Decreased	
Lymphoma	Khalifa KA et al., 2014	$CD14^{+}HLA\text{-}DR^{low/-}$ monocytes	A significant elevation; associated with disease stage, aggressive pathology, recurrence, and treatment-refractory disease	[93]
Juvenile myelomonocytic leukemia (JMML)	Werner J et al., 2025	$CD34^{+}CD38^{-}$ and $CD34^{+}CD38^{+}$ cells	Significantly higher	[97]
NDMM (newly diagnosed MM)	Peng F et al., 2025	CCR2+ inflammatory intermediate monocytes	An increased proportion	[98]

enhancing the angiogenic and immunosuppressive functions of monocytes [23].

Among patients with nasopharyngeal carcinoma (NPC) receiving chemotherapy, the lymphocyte-to-monocyte ratio (LMR) had been demonstrated as a prognostic indicator, since those with an elevated LMR exhibited improved survival outcomes [24]. Additionally, in primary surgically treated HNSCC patients, LMR was more closely associated with event-free survival (EFS), thus it was considered to be a good prognostic indicator [25]. These markers are readily accessible and, in the era of personalized patient care and precision medicine, they may serve as additional risk stratification tools for patients with HNSCC, and help bring more therapeutic strategies that might support monocyte populations with beneficial effects in pathological conditions and inhibit subsets contributing to disease development.

Monocyte subsets and breast cancer

According to Gao ZJ et al. [26], the $CD14^+CD16^+$ monocyte subpopulation can be induced and expanded in breast cancer patients, which is consistent with the previous report that the frequency of $CD14^+CD16^+$ monocyte was increased spontaneously in patients with metastatic gastrointestinal carcinoma [27]. More importantly, it's demonstrated that the levels of $CD14^+CD16^+$ monocytes were significantly negatively associated with tumor size and staging [28], which may have clinical application value to the early diagnosis of breast cancer. Additionally, $CD14^+HLA\text{-}DR^-$ cells derived from breast cancer patients were present at higher levels and proved to produce excessive reactive oxygen species (ROS) to exhibit potent suppressive effects on autologous T cell proliferation, even in individuals with early-stage disease [29]. These results encourage the potential use of strategies targeting $CD14^+HLA\text{-}DR^-$ cells in breast cancer as antioxidant treatment strategies. Simultaneously, breast cancer patients showed a reduction in the secretion of crucial cytokines such as IL-1β, IL-6, and TNF-α by peripheral blood mononuclear cells [30], which was closely linked to the function of monocytes. Breast cancer patients with impaired peripheral blood monocyte response to IFN-γ signaling were more prone to relapse, potentially attributed to the reduced phosphorylation level of STAT1 induced by IFN-γ [31], which may act as predictors of the risk of future relapse in breast cancer patients. It was found that glucose metabolism in the tumor microenvironment drives the glycosylation modification of O-GlcNAc, promoting the differentiation of monocytes into pro-tumor macrophages. This mechanism was verified in the breast cancer model (MMTV-PyMT) [32].

Research has demonstrated notable alterations in the quantity and functionality of monocytes during cancer therapy. In HER2-enriched breast cancer patients under neoadjuvant chemotherapy (NAC), the levels of classical monocytes exhibited a positive correlation with plasma IL-10 concentrations [33], which supported the notion that monocyte subsets and IL-10 could be applied as novel indicators of NAC efficacy in $HER2^+$ BC patients. In triple-negative breast cancer patients, treatment with nanoparticle albumin-bound paclitaxel for 12 weeks resulted in a significant reduction in the numbers of classical, non-classical, and intermediate monocytes [34], this is ostensibly ascribable to the situation that chemotherapeutic agents actuated the body's immune system and expedited the proliferation of bone marrow monocytes. Another study found that the average number and phagocytic activity of monocytes in breast cancer patients exhibited a postoperative increase, ultimately reaching the pre-treatment control level [35]. In addition, breast cancer patients with bone metastasis showed significant changes in the number and proportion of peripheral blood monocytes before and after receiving zoledronic acid treatment, particularly an increase of $CD14^+CD23^+$, $CD14^+CD23^-$, and $CD14^+CD123^-$ monocytes [36]. Conversely, a decrease was noted in the count of $CD14^{low}CD23^+$ cells compared to $CD14^{low}CD123^+$ cells, suggesting that diphosphonate treatment could impact monocyte-mediated immune response [36]. These findings may impact the immune status of breast cancer patients and potentially correlate with therapeutic efficacy.

Monocyte subsets and lung cancer

Intravascular cell labeling, cell transplantation, and fate mapping studies established that classical $CD14^{++}CD16^-$ monocytes served as circulating precursors for lung tissue mono-

cytes as well as interstitial and alveolar macrophages. In contrast, non-classical $CD14^{+}CD16^{++}$ monocytes were confined to pulmonary vessels and gave rise to a distinct population of pulmonary intravascular macrophages [37].

It was reported that both the frequency and absolute number of classical and intermediate monocytes were significantly increased in the peripheral blood of non-small cell lung cancer (NSCLC) patients compared with that of the healthy subjects [38]. The surface expression of $CD11C^{+}$ and $HLA\text{-}DR^{+}$ on intermediate monocytes positively correlated with the number of macrophages in the tumor microenvironment (TME) of lung cancer [38], which may indicate the role of these cells in cancer immunity. Moreover, a higher percentage of monocytes with low CD62L expression was observed, while those exhibiting high CD62L expression were more prone to migrate to lymph nodes and tissues and differentiate into diverse antigen-presenting cells [38]. Consequently, these findings implied the potential involvement of monocytes in dampening anti-cancer responses. The expression of CXCL8 and IL1β in monocytes can predict which patients with NSCLC are at risk of developing irAE (immune-related adverse events), especially those with severe cases [39]. Another study showed that $CD14^{+}$ monocytes in the TME of non-small cell lung cancer patients revealed a dysfunctional phenotype, which presented as lower HLA-DR expression and reduced granzyme B, and pro-inflammatory cytokines [40]. This observation implied that diminished monocyte HLA-DR expression in lung cancer patients may facilitate tumor-induced immune suppression and consequently represent a potential target for therapeutic intervention. Another study revealed that among six inflammatory scoring indices, the LMR demonstrated the highest predictive value for prognosis in NSCLC patients. LMR > 0.2 was identified as a significant risk factor for both OS (Overall Survival) and PFS (Progression-Free Survival) [41]. Xue R et al. presented that $CD16^{+}$ monocytes in the peripheral blood of NSCLC patients exhibited elevated levels of Tie2 expression, and they were frequently localized in close proximity to blood vessels [42], implying their potential involvement in tumor angiogenesis. In addition, NSCLC patients with increased frequencies of Tie2-expressing monocytes demonstrated compromised pulmonary function and diminished survival rates [42]. Patients diagnosed with lung squamous carcinomas (LUSC) exhibited heightened levels of factor XIIIA in inflammatory monocytes ($CCR2^{High}CD14^{+}CD16^{Low}$), which provided a pro-tumor and pro-metastatic micro-environment and had a high immunosuppressive effect [43]. The proportion of classical monocytes ($CD14^{+}CD16^{-}$) in LUSC was also high [44]. Ultimately, these factors contributed to unfavorable survival outcomes in affected individuals.

Studies showed that the combination of etoposide and cisplatin induced an elevation in the population of $IL\text{-}10^{+}CD206^{+}CD14^{+}$ M2-like monocytes in the peripheral blood of patients with small cell lung cancer (SCLC) when compared to untreated patients [45]. Before platinum-based chemotherapy, patients with lung adenocarcinoma demonstrated decreased levels of classical and intermediate $HLA\text{-}DR^{+}$ monocytes in comparison to healthy individuals. Following chemotherapy, there was a notable increase in the proportion of classical and intermediate monocytes, while that of non-classical monocytes remained unchanged [46]. These results suggested that the elevation of classical and intermediate $HLA\text{-}DR^{+}$ monocytes after chemotherapy may indicate immunosuppression in advanced lung adenocarcinoma, since only monocytes producing phagocytes and IL-10 exhibited an increase, whereas those producing proinflammatory cytokines showed no significant alteration [46].

Monocyte subsets and colorectal cancer

Previous studies had reported a positive correlation between the overall proportion of peripheral blood monocytes in colorectal cancer (CRC) patients and their TNM staging, tumor differentiation degree, as well as the likelihood of lymph node metastasis [47]. $CD14^{+}$ monocytes were the most enriched subpopulation in the peripheral blood of CRC patients [48]. The accumulation of $CD14^{+}CD169^{+}$ monocytes in tumor tissue among colorectal cancer patients was prone to be associated with the pathogenic stage and positively correlated with serum levels of IL-10 and CEA [49]. New research found that a lower ratio of cytotoxic lymphocyte: monocytic lineage cells was associated with cancer recurrence. Gene Ontology analysis

revealed that pathways associated with protumoral extracellular matrix remodeling were suppressed in tumors exhibiting a high cytotoxic lymphocyte: monocytic lineage ratio, suggesting a diminished propensity for tumor progression [50]. The monocyte to high-density lipoprotein ratio (MHR), a validated inflammatory marker extensively utilized in cardiovascular diseases, has also been applied across various diseases [51]. It can be used as a reliable clinical indicator to assess the body's cholesterol metabolism. Recent findings suggest that an increasing MHR is an independent risk factor for CRC [52].

Within the $CD14^+$ population, mature $CD14^+$ $HLA\text{-}DR^+$ cells exhibited a closer proximity to tumor cells compared to their immature counterparts, characterized by $CD14^+$ $HLA\text{-}DR^-$ expression. However, the presence of $CD14^+$ $HLA\text{-}DR^+$ cells was associated with prolonged survival in both intraepithelial and stromal compartments, while the adverse prognostic impact of $CD14^+$ $HLA\text{-}DR^-$ cells was only observed within the intraepithelial compartment. This suggested that the significance of immature $HLA\text{-}DR^-$ subsets may rely on their close interaction with tumor cells [53]. These results supported the multimarker evaluation of myeloid immune infiltrates as a robust, quantitative prognostic tool in colorectal cancer. Extracellular vesicles (EVs) secreted by CRC tumor cells can be absorbed by bone marrow-derived monocytes and facilitate their differentiation into inhibitory phenotypes. The exposure of monocytes to tumor-derived EVs led to the downregulation of MHC class II and co-stimulatory molecules while augmenting the expression of PD-L1. More importantly, its capacity to activate antigen-specific $CD4^+$ T cell responses was diminished [54], thereby facilitating immune evasion. The endogenous selectin ligand PSGL-1 on monocytes was responsible for facilitating the selective recruitment of monocytes to metastatic sites [55], thereby promoting efficient survival, extravasation, and metastasis of colorectal cancer cells. Therefore, we can detect the level of the endogenous selectin ligands, particularly PSGL-1 to predict the prognosis of CRC patients.

Anti-VEGFR2 therapy upregulated the expression of CX3CL1 that recruits $CX3CR1^+$ non-classical monocytes, which subsequently attracted neutrophils via CXCL5, resulting in the formation of an immunosuppressive microenvironment with a reduction of cytotoxic T lymphocytes in the tumor of CRC mice [56]. The multistep process provided multiple points of intervention, so that we can prevent immune suppression and improve the effectiveness of anti-VEGF therapy by modulating the immune microenvironment.

In recent years, meta-analysis had demonstrated a positive correlation between the lymphocyte-to-monocyte ratio in peripheral blood leukocytes of CRC patients and their overall survival (OS) and disease-free survival (DFS) [57]. However, further evidence-based medicine research is required to establish this index as a reliable prognostic indicator for colorectal cancer patients in the future.

Monocyte subsets and primary liver cancer

In human hepatocellular carcinoma (HCC), the peritumoral areas were highly infiltrated with $CD14^+$ monocytes with pro-inflammatory phenotypes (including high expression of HLA-DR, CD86, and production of TNF-α, IL-1β, etc.), while the tumor nests were enriched with $CD14^{low}$ macrophages typically with anti-inflammatory markers such as high expression of IL-10 [58]. It was found that classical monocytes ($CD14^{++}CD16^-$) were significantly increased in immunotherapy responders and may promote anti-tumor immunity [59]. Monocytes were educated by TME to up-regulate their glycolytic activity, resulting in the production of large amounts of CXCL2 and CXCL8 [60]. These chemokines effectively recruited peripheral neutrophils [60], which might subsequently favor tumor metastasis and facilitate disease progression in human HCC. CCL15 was the most abundantly expressed chemokine in HCC and held significant prognostic value. It worked in an autocrine manner to promote tumor invasion, while also recruiting $CCR1^+$ $CD14^+$ monocytes toward HCC invasive margin [61]. These monocytes subsequently inhibited anti-tumor immune responses, facilitated angiogenesis, and expedited tumor invasion and metastasis [61]. The characteristics of the CCL15-CCR1 axis in HCC strongly supported its possibility as a novel therapeutic target. In patients with hepatocellular carcinoma, $S100A9^+CD14^+$ monocytes may promote tumor immune escape

by regulating immunosuppressive pathways and weakening T cell function. The level of S100A9 can not only be used to predict the efficacy of ICB in patients with liver cancer, but also serve as an important indicator for evaluating the prognosis of patients [62].

PD-1 expression was elevated in monocytes from HCC patients [63]. The activation of the glycolytic pathway in monocytes within the TME can facilitate disease progression by inducing an up-regulation of PD-L1, thus rerouting the pro-inflammatory response into an immunosuppressive direction [64], which might represent a novel tumor immune editing strategy and indicate efficient targets for future immune-based anti-cancer therapies. The findings of another study indicated that HCC patients with PD-L1$^+$ PD-L2$^+$ CD14$^+$ cells exhibited a more unfavorable prognosis compared to those with other subtypes of CD14$^+$ cells [65]. Within the tumor microenvironment, CD14$^+$HLA-DR$^{-/low}$ cells contribute to CD8$^+$ T cell exhaustion through the sustained expression of immunosuppressive molecules, such as PD-L1. In hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC), HLA-DR$^+$ tumor cells are significantly associated with the CD8$^+$ T cell exhaustion state, thereby fostering a distinct immune-evasive microenvironment [66].

The myeloid-derived suppressor cell (MDSC) population predominantly resided within the TME, facilitating immune evasion and attenuating the cytotoxicity of immune cells, thereby conferring resistance to immunotherapy [67]. Monocytes can differentiate into such suppressive cells under specific conditions, elucidating certain aspects of tumor immune escape. According to relevant studies, the proportion of CD14$^+$HLA-DR$^-$MDSCs in the peripheral blood of liver cancer patients was significantly higher compared to that of chronic hepatitis B patients and healthy individuals [68]. The proliferation and cytokine secretion of T cells was inhibited by CD14$^+$HLA-DR$^-$MDSCs [68]. Patients with a high MDSC proportion not only exhibited an increased risk of relapse but also experienced shorter overall survival [68], indicating the necessity for clinicians to develop more optimized treatment regimens and closely monitor these tumor types. The frequency of MDSCs was significantly increased in patients with HCC and exhibited a positive correlation with tumor stage, size, burden, and Child-Pugh grade, but not with biochemical parameters of liver function [69]. On the contrary, the proportion of MDSCs in the peripheral blood of patients with HCC undergoing radiotherapy not only decreased but also exhibited a negative correlation with overall patient survival [69]. Within the fibrotic liver microenvironment, TGF-β induces the high expression of PPP1R15A in monocytic myeloid-derived suppressor cells (M-MDSCs). PPP1R15A subsequently upregulates immunosuppressive molecules (e.g., ARG1, S100A8/A9, ROS) in these cells, thereby suppressing T cell function and promoting tumor immune escape [70]. The aforementioned suppressive cells, including monocytes, constituted an unfavorable factor that facilitated the progression, recurrence, and metastasis of HCC.

Monocyte subsets and melanoma

Chavan et al. [71] reported a decrease in the count of CD14$^+$CD16$^-$ classical monocytes with 18 cases of stage IV melanoma. An elevated number of slan$^+$ (6-sulfo LacNAc) non-classical monocytes (slanMo) was observed in the peripheral blood of patients with early-stage melanoma [72]. Co-culture experiments of slanMo cells and NK cells revealed that the co-culture was required to facilitate IFN-γ and TNF-α production-reaching levels capable of limiting melanoma growth and inducing tumor cell senescence [72]. Therefore, enhancing the interaction between slanMo cells and NK cells can synergistically enhance melanoma cell killing. In vitro, inflammatory monocytes impeded melanoma cell proliferation through a reactive oxygen species-dependent mechanism, while both their depletion and neutralization of reactive oxygen species enhanced tumor cell dissemination in vivo [73]. Furthermore, regulatory CD4$^+$ T cells contributed to tumor progression also by partially inhibiting the recruitment and differentiation of inflammatory monocytes in the skin of melanoma patients [73]. Prior to initiating PD-1 inhibitor therapy, the level of CD14$^+$CD16$^-$HLA-DR^{high} monocytes in peripheral blood served as the strongest independent predictor of PFS and OS in melanoma patients [74].

Single-cell RNA sequencing (scRNA-seq) analysis revealed that CD244$^-$ monocytes exhibit significantly increased gene expression associ-

ated with antigen processing, phagocytosis, and autophagy. Clinical data further indicated that $CD244^-$ monocyte levels are associated with improved survival rates in melanoma patients [75]. In melanoma patients, a specific group of microRNAs had been found to be associated with MDSCs and resistance to immunotherapy. These microRNAs played a crucial role in the conversion of monocytes into MDSCs, and their expression levels were significantly elevated in $CD14^+$ monocytes isolated from peripheral blood samples of patients [76]. Additionally, Inhibitor of differentiation 1 (ID1) might be a possible therapeutic target to deactivate monocytic MDSC and direct myeloid differentiation towards a less immunosuppressive and more immunogenic phenotype [77].

During immunotherapy, a substantial population of CD103+ monocytes emerged in murine melanoma tumors via direct differentiation of Ly6C+ monocytic precursors [78]. However, this differentiation process was controlled by the activation of p53, which drove the up-regulation of Batf3 and the acquisition of the Ly6C+CD103+ phenotype [78]. Augmenting p53 expression using pharmacological agonists resulted in a sustained increase in Ly6C+CD103+ cells within tumors during immunotherapy, leading to improved efficacy and duration of response [78]. Therefore, targeting p53-driven differentiation of Ly6C+CD103+ monocytes represents a potent and previously unrecognized strategy for enhancing immunotherapeutic outcomes. Experiments in a murine melanoma model demonstrated that inflammatory monocytes constituted up to 40% of the tumor microenvironment in treatment-naïve tumors, whereas their proportion was significantly reduced to approximately 10% in therapy-resistant tumors. This differential distribution suggests an indispensable role for inflammatory monocytes in maintaining local anti-tumor immune responses [79].

Monocyte subsets and ovarian cancer

A higher percentage of monocytes in peripheral blood was revealed in patients with OC relative to normal patients through CIBERSORT analysis [80]. A sudden increase in intermediate monocytes had been observed in the ascites of ovarian cancer patients, which was believed to be associated with a reduction in effector T cell content and the presence of soluble immunosuppressive mediators [81]. Furthermore, this abrupt rise in intermediate monocytes showed a positive correlation with $CCR2^{hi}CD163^{hi}$ $CD206^{hi}$ macrophages and tumor burden in the peritoneum, suggesting that these cells were linked to immunosuppression and tumor burden [81], which could serve as an evaluation index for assessing immune status in ovarian cancer patients with malignant ascites. In addition, there was a significant increase in Tie2 expressing monocytes (TEM) observed in the peripheral blood, ascites, and tissue samples of patients with ovarian cancer [82]. Elevated levels of Ang2 were detected in ovarian cancer ascites and found to attract TEM towards tumor tissue [82]. Notably, upon stimulation by Ang2, TEMs promoted angiogenesis through the IGF1 signaling pathway both in vivo and in vitro experimental models [82]. Therefore, targeting the Ang2-TEMs-IGF1 axis holds promise as a new therapeutic strategy for treating ovarian cancer.

Before chemotherapy in ovarian cancer patients, not only the proportion of $CD14^+HLA\text{-}DR^-$ monocytes significantly increased, but also the likelihood of advanced tumor development in such patients increased by 3.33 times [83]. However, following chemotherapy administration, there was a decrease of 2.02% in the median number of $CD14^+HLA\text{-}DR^-$ monocytes in the peripheral blood of patients with advanced ovarian cancer [83]. These findings suggest that anticancer drugs possess inhibitory effects on the proliferation of $CD14^+HLA\text{-}DR^-$ monocytes and provide support for the notion that $CD14^+HLA\text{-}DR^-$ monocytes contribute to the progress of ovarian cancer.

Monocyte subsets and oral squamous cell carcinoma

The percentage of $CD14^+CD16^+$ intermediate monocytes in the peripheral blood of patients with oral squamous cell carcinoma was significantly higher than that of healthy volunteers [84]. Conversely, there was a decrease of $CD14^+CD16^-$ classical monocytes, while no significant change was observed in the proportion of $CD14^{low}CD16^+$ non-classical monocytes [84]. These findings suggest a potential association between $CD14^+CD16^+$ intermediate monocytes

and the development of oral squamous cell carcinoma.

Monocyte subsets and pancreatic cancer

Patients with pancreatic cancer (PC) exhibited an elevated peripheral blood monocyte count, while the number of bone marrow monocytes was reduced, which was facilitated by CCL2-mediated mobilization of monocytes from the bone marrow [85]. Compared to $CD14^{++}CD16^{-}$ cells, $CD14^{+}CD16^{++}$ cells released more TNF-αand IL-12 upon stimulation by tumor cells. In patients with pancreatic cancer, monocyte activation was stimulated by the production of cytokines (TNF-α, IL-10, IL-12) and chemokines from tumor-derived microvesicles (TMV) and tumor cells. Notably, the predominant subset of monocytes involved in anti-tumor response was represented by $CD14^{+}CD16^{++}$ cells due to their capacity for generating cytotoxic and pro-inflammatory cytokines [86]. In pancreatic cancer, Schwann cells mediate the recruitment of inflammatory monocytes through the secretion of neurotrophic factors and the chemokine CCL2, thereby inducing tumor cell migration and invasion [87].

There was compelling evidence suggesting that pancreatic cancer cells possessed the capability to secrete pro-inflammatory metabolic substances, which subsequently induced alterations in normal hematopoietic stem cells and promoted the accumulation of myeloid-derived suppressive cells within both the circulation and TME [88]. The abundance of these suppressive cells exhibited a negative correlation with overall survival among patients with pancreatic cancer, where higher proportions were associated with an increased likelihood of metastasis occurrence [88]. However, it should be noted that the immunosuppressive activity attributed to myeloid-derived suppressive cells was only observed in a subset of patients and predominantly manifests within the monocyte subpopulation. Transcriptome analysis conducted on these immunosuppressive cells has revealed the critical involvement of the STAT3 gene in mediating gene rearrangement specifically within monocytes [88]. In patients with pancreatic cancer, the proportion of inhibitory monocytes ($CD14^{+}HLA\text{-}DR^{-}$) in peripheral blood increased, and the level of $CD14^{+}$ monocytes was positively correlated with the level of $CD14^{+}HLA\text{-}DR^{-}$. The downregulation of HLA-DR expression on monocyte surface was achieved through interaction between exosomes derived from pancreatic cancer cells and monocytes. Pancreatic cancer-derived exosomes can induce arginase synthesis and generation of reactive oxygen species by modulating the STAT3 signaling pathway [89], thereby suppressing immune function in monocytes. Protein levels of IL-1β were low in circulating monocytes from HDs but increased substantially upon recruitment to tumors. Analysis of patient scRNA-seq data highlighted tumor monocytes as the major source of IL-1β in human pancreatic ductal adenocarcinoma (PDAC). Antibody-mediated targeting of IL-1β in vivo led to reduced IL-1β expression by monocytes, concomitant with delayed PDAC growth and increased activation of cytotoxic T cells in draining lymph nodes [90]. These results provided novel mechanistic insight into a highly immunosuppressive environment. Understanding monocyte-exosome interactions could lead to novel immunotherapies for PC.

Monocyte subsets and hematological malignancy

Matthew T. et al. observed a significant increase in $CD14^{+}CD16^{++}$ non-classical monocytes and significant reduction of $CD14^{++}CD16^{-}$ classical monocytes within the myeloid-enriched compartment at B-ALL diagnosis when compared with healthy controls [91]. Studies have shown that classical and intermediate monocytes accumulated in the peripheral blood of patients with diffuse large B-cell lymphoma (DLBCL) and exhibited an inflammatory phenotype, whereas there was a decrease in the frequency of non-classical monocytes within the peripheral blood [92]. The findings of another study revealed a significant elevation in the proportion of $CD14^{+}HLA\text{-}DR^{low/-}$ monocytes among lymphoma patients compared to healthy controls. Moreover, it was observed that patients with advanced disease stage, aggressive pathology, recurrence, and treatment-refractory disease commonly exhibited an increase in $CD14^{+}$ monocytes and deficiency in HLA expression [93]. Therefore, devising therapeutic strategies to overcome these inhibitory properties of monocytes holds potential value.

There is a report described the first documented case of chronic myelomonocytic leukemia (CMML) concurrent with IgA vasculitis. Skin

biopsy revealed IgA deposition within small vessels, implicating monocyte involvement in the pathogenesis of vasculitis. A concurrent NRAS mutation was identified as a potential shared driver of both conditions [94]. Integrated ATAC-seq and RNA-seq analyses revealed extensive dysregulation of enhancer regions (marked by H3K27ac) in monocytes from CMML patients. This epigenetic alteration led to suppression of the NF-κB signaling pathway and enhanced mitochondrial oxidative phosphorylation (OxPhos) activity, which collectively promoted their polarization toward an M2-like macrophage phenotype. This cellular reprogramming occured concomitantly with a Th1/Th2 immune imbalance [95]. Juvenile myelomonocytic leukemia (JMML) is an aggressive hematologic malignancy with myeloproliferative characteristics that affects young children and is associated with significant morbidity and mortality [96]. Juwita Werner et al. observed that the percentage of $CD34^+CD38^-$ and $CD34^+CD38^+$ cells was significantly higher in peripheral blood mononuclear cells (MNCs) of JMML patients compared to healthy controls, and higher CLL-1 expression in JMML $CD34^+$ cells compared to healthy control $CD34^+$ cells. CLL-1 expression was more heterogeneous compared to healthy controls. These preclinical data support the development and clinical investigation of CLL1-targeting immunotherapy in children with relapsed/refractory JMML [97].

Patients with NDMM (newly diagnosed MM) had an increased proportion of CCR2+ inflammatory intermediate monocytes in the bone marrow compared with HCs. The proportion of CCR2- intermediate monocytes was higher in patients with NDMM than in HCs [98].

Summary and prospect

Tumor and the body's immune system engage in a continuous action and prolonged struggle. Within the TME, various immune cells, such as monocytes, macrophages, and lymphocytes, play significant roles. Current reports have confirmed that tumor-associated macrophages contribute to immunosuppression, fostering tumor progression and metastasis. With consensus pointing towards the differentiation of peripheral blood monocytes as the origin of tissue macrophages, the question arises: whether monocytes in peripheral blood, as the precursor of macrophages, also participate in the immune response of tumors and play an important role is bound to arouse the research interest of most scholars.

The tumor microenvironment, comprising diverse cells and matrices, introduces variability in how circulating monocytes reach the tumor site. Whether tumor-secreted factors or the microenvironment influence monocyte arrival and modify their phenotypic function needs further exploration. Based on the above research results on monocytes in common tumors, it can be concluded that in various common tumors, the proportion and functional phenotype of peripheral blood monocytes subsets will change, affecting the immune response of the body, which is not only related to tumor invasion and metastasis, but also related to the clinical prognosis of patients.

An expanding body of evidence suggests that peripheral blood monocytes can serve as biomarkers for predicting, diagnosing, and prognosing cancer in patients. The simplicity of obtaining monocytes from patient blood samples makes this procedure feasible. Understanding the intricate relationship between monocytes and tumors presents a promising avenue for clinical oncology diagnosis and treatment. Notably, immunosuppressive monocytes circulating in cancer patients are linked to a higher proportion of poor prognoses, emphasizing the crucial role of these cells in tumor dynamics.

A high proportion of monocytes have an inhibitory effect on tumor growth, especially for advanced malignant tumors with blood metastasis, and can effectively kill tumor cells in circulation. Therefore, monocytes can recognize and kill tumor cells as early as possible before tumor cells metastasize to other sites, so as to inhibit tumor metastasis and localize tumors, which is beneficial to treatment. If methods can be developed to enhance the activity of monocytes, this is also a new strategy for anti-tumor, which can help to inhibit tumor progression and recurrence.

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Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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