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**HEALTH SCIENCES**

# Extracellular vesicles as modulators of monocyte and macrophage function in tumors

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**Abstract:** The tumor microenvironment (TME) harbors several cell types, such as tumor cells, immune cells, and non-immune cells. These cells communicate through several mechanisms, such as cell-cell contact, cytokines, chemokines, and extracellular vesicles (EVs). Tumor-derived vesicles are known to have the ability to modulate the immune response. Monocytes are a subset of circulating innate immune cells and play a crucial role in immune surveillance, being recruited to tissues where they differentiate into macrophages. In the context of tumors, it has been observed that tumor cells can attract monocytes to the TME and induce their differentiation into tumor-associated macrophages with a pro-tumor phenotype. Tumor–derived EVs have emerged as essential structures mediating this process. Through the transfer of specific molecules and signaling factors, tumor-derived EVs can shape the phenotype and function of monocytes, inducing the expression of cytokines and molecules by these cells, thus modulating the TME towards an immunosuppressive environment.

**Key words:** Monocytes, extracellular vesicles, immunophenotype, immunomodulation, tumor-associated macrophages.

## INTRODUCTION

The TME is a complex system that harbors cancer cells, stromal cells, immune cells, and extracellular components. During tumor development, leukocyte recruitment, angiogenesis, and tissue remodeling occur (Baghban et al. 2020). Among the cells participating in TME, one may highlight monocytes, tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs). These cells interact with cancer cells, leading to the release of extracellular matrix (ECM), matrix metalloproteinase (MMPs), chemokines, EVs, and growth factors, which sustain the microenvironment and contribute to cancer progression (Ren et al. 2018). Monocytes are cells of the innate immune system belonging to the mononuclear phagocytic system with high plasticity (van Furth & Cohn 1968), participating in various mechanisms such as immunotolerance, angiogenesis, and the establishment of TAMs (Ugel et al. 2021, Ding et al. 2016). TAMs are the most abundant immune population in TME, whose density is related to a worse prognosis in different types of cancer (Medrek et al. 2012, Fan et al. 2014, Fridman et al. 2017). The ability of monocytes and macrophages to mediate interactions between immune and tumor cells is critical for tumor progression. In addition, monocytes and TAMs can also uptake EVs, influencing cellular response and tumor progression(Nielsen & Schmid 2017). Therefore, the presence of monocytes and TAMs in the TME is an essential indication for tumor progression and can be used as a prognostic factor.

## Abbreviations

BC Breast cancer
ECM Extracellular matrix
EMT Epithelial-mesenchymal transition
ESCRT Endosomal sorting complexes required for transport
EVs Extracellular vesicles
GC Gastric cancer
HCC Hepatocellular carcinoma
HSPs Heat shock proteins
ILVs Intraluminal vesicles
lncRNAs Long non-coding RNAs
lVEs Large vesicles
MDSCs Myeloid-derived suppressor cells
MMPs Matrix metalloproteinase
MVB Multivesicular bodies
NBL Neuroblastoma
ncRNAs Non-coding RNAs
PC Pancreatic cancer
scRNA-Seq Single-cell RNA sequencing
sVEs Small vesicles
TAMs Tumor-associated macrophages
TEMs Tie2-expressing monocytes
TME Tumor microenvironment
TNBC Triple-negative breast cancer

## Phenotypes of monocytes and macrophage

Two monocyte populations were initially described in humans according to their surface markers, CD14 and CD16, described as receptors for LPS and Fcγ-III, respectively(Geissmann et al. 2003). This statement was revised, and three subsets of monocytes are currently described. The classical $CD14^{++}CD16^{-}$ monocytes' subset express high levels of CCR2 and migrate to tissues, where they differentiate into macrophages or dendritic cells. This subset comprises approximately 80-90% of the total monocyte population. The $CD14^{+}CD16^{+}$ intermediate subset, accounting for about 5% of monocytes, exhibits a strong TNF-α response when stimulated with LPS and expresses high levels of CCR5 (Hijdra et al. 2013). The non-classical $CD14^{dim}CD16+$ subset expresses CX3CR1 (Geissmann et al. 2003) and patrols the vascular endothelium, resolving inflammation (Devêvre et al. 2015, Kapellos et al. 2019). This subset represents approximately 7% of monocyte subtypes. Additionally, Tie2-expressing monocytes (TEMs), a distinct $CD14^{+}CD16^{+}$ subpopulation, constitute around 2% of circulating monocytes (De Palma et al. 2005). TEMs do not express CCR2, suggesting that different mechanisms govern their recruitment than monocytes dependent on CCL2. This subpopulation is associated with angiogenesis induction and tumor growth (Lewis et al. 2007, Murdoch et al. 2007). In mice, peripheral blood monocytes can be divided into classic $Ly6C^{high/+}CD43^{+}$ and non-classical patrolling monocytes $Ly6C^{low/-}CD43^{high/+}$ (Ziegler-Heitbrock et al. 2010). It has been shown that at steady state, $LyC6^{high/+}$ monocytes differentiate into $Ly6C^{low/-}$ monocytes, responsible for patrolling the endothelium of small blood vessels by binding to it through CX3CR1 receptor depending on LAF-1/ICAM1(Yang et al. 2014). Through fate mapping, Patel et al. (2017) demonstrated that human classical monocytes grafted onto humanized mice differentiate into intermediate monocytes after 24 hours and non-classical monocytes after 96 hours (Patel et al. 2017). Classic murine monocytes recruited by CCL2 have been linked to a role in promoting breast cancer metastasis, while non-classical monocytes trigger NK cell anti-metastatic activity after detecting circulating metastatic cells and eliminating their debris within blood vessels(Qian et al. 2011, Hanna et al. 2015).

Macrophages are traditionally divided into two activation profiles: the classically activated, pro-inflammatory M1 - with markers such as HLA-DR, CD80/CD86 - and the alternatively activated, anti-inflammatory type M2 -with

features such as CD206 and CD163(Zhou et al. 2020). Evidence from the literature suggests that TME is enriched with TAMs resembling the M2 macrophage profile, responsible for releasing chemokines such as CCL2, capable of recruiting more monocytes for TME (Mantovani et al. 2010). This crosstalk is essential for maintaining this cell type and supporting tumor progression, thus promoting tumor growth, invasion, metastasis, and drug resistance (DeNardo & Ruffell 2019). Myeloid-derived suppressor cells (MDSCs), related to TAMs, were the first cell population described in mice to inhibit the host immune response (Gabrilovich et al. 1998). In mice, they can be classified into two subpopulations: polymorphonuclear MDSCs (PMN-MDSCs) with $CD11b^{+}Ly6G^{hi}Ly6C^{-/low}$ and monocyte MDSCs (M-MDSCs) with $CD11b^{+}Ly6G^{-/low}Ly6C^{hi}$ (Bronte et al. 2016). In humans, M-MDSCs are defined as $CD14^{+}CD33^{+}CD11b^{+}$ HLA-$DR^{-}$ (Hegde et al. 2021). MDSCs play a crucial role in promoting tumor immune evasion. They consume amino acids necessary for T cell proliferation, leading to cell cycle arrest and decreased TCR expression. MDSCs also limit cysteine uptake by T cells, restricting their activation (Srivastava et al. 2010). Additionally, overexpression of indoleamine 2,3-dioxygenase (IDO) within the tumor microenvironment supports MDSCs and contributes to immunosuppression(Prendergast et al. 2018).

Single-cell gene expression analysis showed that $CD14^{++}CD16^{-}$ monocytes expressed more genes associated with phagocytosis and migration functions. In contrast, intermediate monocytes were related to antigen presentation, co-stimulation, and activation of NK and $CD8^{+}$ T cells(Gren et al. 2015, Kapellos et al. 2019). In a single-cell RNA sequencing (scRNA-Seq) study conducted by Villani et al. (2017), 372 monocytes were profiled, demonstrating four distinct clusters. The two largest groups represented classical and non-classical monocytes. In contrast, the remaining two represented monocytes derived from the intermediate subtype, indicating that this population may be less homogeneous, thus revealing potential new monocyte subtypes(Villani et al. 2017). On the other hand, Zilionis et al. (2019) identified only three monocyte gene signatures conserved between human and mouse species(Zilionis et al. 2019). A study analyzing 175 immune cells from 11 patients with breast cancer identified a macrophage subset exhibiting immunosuppressive characteristics, presenting an M2 phenotype (Chung et al. 2017). However, scRNAseq studies have shown that the behavior of TAMs does not correspond to the classic M1/M2 polarization axis. Wagner et al. (2019) identified 19 myeloid clusters within the TME of breast cancer through scRNAseq analysis. Of these, two groups of $CD14^{++}CD16^{-}$ monocytes, two groups of $CD14^{int}CD16^{+}$ monocytes, four groups of migrant macrophages, four groups of resident macrophages, and six groups of TAMs were identified, indicating heterogeneity between the macrophage populations present in this cancer(Wagner et al. 2019). In another study, it was determined that all three clusters of TAMs identified in scRNAseq were among the monocytic clusters that displayed the highest expression of the M2 canonical signature but also showed increased expression of the M1 gene signature. Hence, these single-cell studies have demonstrated divergences between establishing the M1/M2 axis to classify TAMs.

In the TME, monocytes, TAMs, and MDSCs are present in varying proportions depending on the type of carcinoma and degree of progression (Davidov et al. 2020). These studies have highlighted the importance of identifying and accurately characterizing the monocyte and macrophage populations present within TME since each subpopulation can have distinct

functions and behaviors, thus impacting tumor progression differently(Larionova et al. 2020, Mantovani et al. 2017, Zhu et al. 2017).

## Extracellular vesicles

Extracellular vesicles (EVs) are nanostructures delimited by a lipid bilayer known to deliver functional mRNAs, non-coding RNAs (ncRNAs) such as microRNAs (miRNAs), and long non-coding RNAs (lncRNAs); proteins, receptors, and growth factors from diverse cell types to target cells participating in cell signaling by mediating intercellular communication (van Niel et al. 2018, Pathan et al. 2019). EVs are heterogeneous regarding their biogenesis, size, and content (Cocucci & Meldolesi 2015). Large vesicles (lVEs) are formed through plasma membrane budding and subsequent fission. They are commonly referred to in the literature as microvesicles, ectosomes, microparticles, and exovesicles (Théry et al. 2009). They were firstly described as derived from the membrane of platelets (Heijnen et al. 1999), tumors (Al-Nedawi et al. 2008), neutrophils (Hess et al. 1999), and dendritic cells (Obregon et al. 2006). On the other hand, small vesicles (sVEs) are secreted after the fusion of the internal compartments containing intraluminal vesicles (ILVs) with the plasma membrane. They are called exosomes, nanoparticles, or vesicle-type exosomes (Théry et al. 2009). The release of tumor-derived EVs occurs both *in vitro* and *in vivo* and is linked to various processes such as proliferation, activation, apoptosis, and migration of tumor cells (Sung et al. 2021, Phetfong et al. 2022, Andreola et al. 2002). This release is also associated with tumor progression, where highly metastatic tumors release more EVS than those with low metastatic ability (Friedl et al. 1997, Poste & Nicolson 1980, Kalluri 2016).

### *Large vesicles*

The lVEs are produced through plasma membrane protrusion followed by fission. This process requires rearrangements of membrane lipids and is initiated by increasing intracellular calcium levels and activating calpain, the protease responsible for separating membrane proteins from the cytoskeleton (Pasquet et al. 1996). Consequently, there is a remodeling of the actin filaments, allowing the occurrence of bubbles, with the release of vesicles through microdomains of the plasma membrane known as lipid rafts (Ståhl et al. 2019, Del Conde et al. 2005). Muralidharan-Chari et al. (2009) demonstrated the importance of the ARF6 protein in the release of microvesicles once the endosomal complex regulated by ARF6 is crucial in the selective incorporation of molecular charge in these structures(D'Souza-Schorey & Chavrier 2006, Muralidharan-Chari et al. 2009). ARF6 targets include ERK and MLCK, important regulators of actin polymerization and myosin activity, both essential for releasing microvesicles (Minciacchi et al. 2015, Muralidharan-Chari et al. 2009).

### *Small vesicles*

The characterization and study of exosome origin are widely discussed in the literature. The process of exosome formation begins with the invagination of the plasma membrane to form endosomes, which are intracellular compartments involved in the screening and degradation of internalized molecules of the extracellular environment. As the endosomes mature, they fuse to form multivesicular bodies (MVB), intermediates of the endosomal system. The formation of exosomes requires the action of endosomal sorting complexes required for transport (ESCRT), which are composed of four proteins that work together to promote the

formation of MVB (James 2015). The mechanism of ESCRT is initiated through the recognition and sequestration of ubiquitinated proteins for specific endosomal domains. After cleavage of the ILVs, the ESCRT-III complex separates from the MVB membrane (Zhang et al. 2019), resulting in the secretion of exosomes through the fusion of these with the plasma membrane.

Exosomes were identified in the 1980s and were initially considered residues resulting from cell damage (Johnstone et al. 1987). Later, the importance of these for intercellular communication in different cellular processes was observed. They participate in various critical biological processes, including immunomodulation, inflammation, angiogenesis, and tumor progression (Kurywchak et al. 2018, Song et al. 2018). They have been studied as potential biomarkers in neurodegenerative diseases, cardiovascular diseases, and cancer, as they may contain valuable information about cell function (Raposo & Stoorvogel 2013). Exosomes have a distinct structure, including proteins, lipids, and RNAs of cellular origin, making them a potential source for biomarker identification and disease therapies.

### *EVs cargo*

Although lVEs and sVEs are structurally similar, they differ in composition. The membrane of the lEVs is enriched in cholesterol and diacylglycerol, exposed phosphatidylserine, and lipid rafts, with membrane-derived receptors, cytokines, chemokines, and lipids (Ståhl et al. 2019, Camussi et al. 2010). Dolo et al. (1998) observed that microvesicles released by breast cancer cells contained proteases such as MMP-2 and MMP-9, and β1 integrin, indicating the importance of EVs release in extracellular matrix proteolysis during cell migration (Dolo et al. 1998). Lischnig et al. (2022) identified that the primary biological functions of lVEs are related to translation initiation, cell-to-cell adhesion, and mitochondrial electron transport, while the main functions of sVEs are associated with the reorganization of the extracellular matrix, cell adhesion, endosomal transport, and nuclear organization. Additionally, lVEs are enriched in ribosomal, mitochondrial, and nuclear proteins and proteins involved in cytokinesis (Lischnig et al. 2022). On the other hand, sVEs are enriched in tetraspanins, ADAMs, and ESCRT-III complex proteins, as well as SNAREs and endosome-associated Rab proteins. Exosomes are rich in proteins such as tetraspanins CD9, CD63, CD81, heat shock proteins (HSP70, HSP90), and MVB-forming proteins that are involved in the release of exosomes such as Alix and TSG101. Furthermore, they have abundant miRNA, lncRNA, and circRNAs (Zhang et al. 2019). Additionally, the content of lVEs can be a source of information for the cellular microenvironment, acting as signals of cellular damage, inflammation, and other processes necessary for a cellular response. The lVEs are also considered essential for cancer progression since they may contain molecules that promote angiogenesis and inhibition of the immune response, among other effects (Loyer et al. 2014, Tricarico et al. 2017)

## Extracellular vesicles within the tumor microenvironment: actions on monocyte and macrophage functions

The interaction of monocytes with the microenvironment is crucial for their migration, differentiation, and action in healthy individuals or under pathophysiological conditions. Cytokines, chemokines, and EVs play a pivotal role in this process. Classic monocytes produce TNFα, IL-6, and IL-1β in response to TLR2 and TLR4 receptor agonists, while the non-classical subtype secretes INF-α in response to intracellular TLR3, TLR7, and TLR8 (Boyette

et al. 2017, Geissmann et al. 2003, Devêvre et al. 2015). IL-6 in TME skew monocyte differentiation into TAM with M2 characteristics, exhibiting $CD14^{high}CD163^{high}CD80^{low}$ phenotype (Duluc et al. 2007). The migration of monocytes to TME is crucial for establishing TAMS depending on the CCR2/CCL2 axis (Kadomoto et al. 2021). Macrophage infiltration into cancer tissues is positively correlated with increased expression of CCL2 (Mizutani et al. 2009). Additionally, CCL2 also has been linked to the recruitment of CCR2+ monocytes to facilitate metastasis in breast cancer (BC) (Qian et al. 2011).

Tumor-derived EVs induce the secretion of TNFα and IL-1β by CD14+ monocytes, activating the NF-kB pathway (Gärtner et al. 2018). Popěna et al. (2018) demonstrated that colorectal cancer-derived EVs can promote changes in the immunophenotype of monocytes and macrophages, increasing CD14+ in M0 and HLA-DR in M1 and M2 macrophages. In addition, the cytokine secretion profile of these cells was altered, resembling the M1 profile in monocytes (Popěna et al. 2018). NcRNAs have been studied in cancer as promoters of invasion, metastasis, and initiation of epithelial-mesenchymal transition (EMT) (Beltran et al. 2008, Xiu et al. 2019, Gupta et al. 2010). In a study analyzing scRNAseq data, colorectal cancer-derived EVs enriched with miR-21-5p and miR-200a promoted immune evasion, one of the hallmarks of cancer, through upregulation of PD-L1 in CD206+ TAMs, being associated with a worse prognosis (Yin et al. 2022). PD-1 is an immunoinhibitory receptor highly expressed on tumor-specific T cells (Ahmadzadeh et al. 2009), which is critical in tumorigenesis. Tumor cells express PD-L1 to evade anti-tumor responses (Juneja et al. 2017) since PD-1/PD-L1 interactions are implicated in T-cell exhaustion and reduced immune response (Veluswamy & Bruder 2018). Glioblastoma (GB)-derived EVs containing PD-L1 induce the formation of immunosuppressive non-classical monocytes that inhibit T cell proliferation *in vitro* (Hines et al. 2020). Moreover, BC cells produce exosomes under endoplasmic reticulum (ER) stress, which contain miR-27a-3p, promoting immune escape by upregulating PD-L1 expression in macrophages by activating the PTIEN/AKT/PI3K pathway (Yao et al. 2020).

It has been shown that GB-derived EVs skew the differentiation of monocytes to M2 macrophages, which acquired characteristics that resemble tumor-supportive phenotype observed in patients. The macrophages presented a decrease in HLA-DR and an increased phagocytic capacity, with an increase in the secretion of IL-6, MCP-1, and VEGF. Glioma with a stem cell-like phenotype also presents a most pronounced modulation of the monocyte to macrophage differentiation (De Vrij et al. 2015). GB-derived exosomes significantly increased the expression of arginase-1, IL-10, and CD206 in macrophages. The reprogrammed macrophages arginase+ produce exosomes that promote glioblastoma progression(Azambuja et al. 2020). PD-L1 expression in gastric cancer (GC) is a decisive factor in evaluating prognosis (Wu et al. 2006). A subset of tumor-associated macrophages, PD1+ macrophages, accumulate in advanced-stage GC and exhibit an M2-like surface profile, with a significant increase in CD206, IL-10, and CCL1 expression, which promotes disease progression. These macrophages have a robust immunosuppressive activity on CD8+ T cells and are associated with tumor progression and early recurrence in GC patients (Wang et al. 2018).

### *Effects of EVs on M-MDSC*

Monocytes exposed to melanoma-derived EVs are converted to M-MDSC, presented decreased HLA-DR expression, and increased IL-6 and CCL2 transcription and secretion, exhibiting suppressive activity on activated T cells.

Genome-wide transcriptional analysis revealed that regulation of these cells involves miRNA modulation and the upregulation of the *CD274/PD-L1* gene. MDSC-miRs are enriched in the plasma of melanoma patients and correlated with resistance to immunotherapy (Huber et al. 2018). In another study, EVs uptake by immature myeloid cells from murine melanoma leads to increased PD-L1 expression both in mRNA and protein levels, accompanied by upregulation of inflammatory and immunosuppressive mediators such as IL-1β, IL-6, IL-10, TNF-α, and COX-2. Melanoma-EV-mediated upregulation of PD-L1 involves TLR signaling through the HSP86/TLR4 axis (Fleming et al. 2019). Activation of TLR2 and -4 after EVs uptaken by macrophage cell lines can stimulate the production of cytokines *in vitro* (Chow et al. 2014, Bretz et al. 2013). Additionally, the BAL fluid obtained from wild-type mice with melanoma was enriched in macrophage compared to TLR4-deficient mice, indicating a possible involvement of TLR4 on macrophage migration(Lee et al. 2010). Furthermore, melanoma exosomes educate bone marrow (BM) progenitors, increasing the frequency of pro-angiogenic c-Kit+Tie2+ cells through MET, which enhances metastasis (Peinado et al. 2012). BC-derived exosomes containing miR-9 and miR-181a promote the development of early-stage MDSCs via inhibition of SOCS3 and PIAS3, respectively. High IL-6 expression is correlated with SOCS3 deficiency-dependent hyperactivation of the JAK/STAT signaling pathway in these cells (Jiang et al. 2020).

Heat shock proteins (HSPs) are found to be highly expressed in human cancers and play a significant role in the proliferation, differentiation, and immune recognition of tumor cells (Ciocca & Calderwood 2005). Tumor-derived exosome-associated HSP72 determines the suppressive activity of the mouse and human MDSCs via activation of STAT3. The TLR2/MyD88 and the STAT3 pathways play a role in MDSC activation by triggering the production of IL-6 and the subsequent activation of STAT3. The ERK pathway, on the other hand, triggers the expansion of MDSCs (Chalmin et al. 2010). Gao et al. (2020) identified that tumor specific-antigen and HSP70 were enriched in renal cancer-derived exosomes, which is responsible for the expansion and activation of MDSCs, leading to the production of ROS and NO, secretion of IL-10 and TGF-β and intense arginase activity. The MDCS treated with these exosomes suppressed the cytotoxic activity of CD8+ T cells (Gao et al. 2020). Tumor-derived exosomes harboring mutp53 shed miR-1246-enriched EVs. The uptake of these exosomes by macrophages induced their reprogramming to a tumor-supportive phenotype with increased secretion of IL-10, TNF-α, and CCL2 (Cooks et al. 2018).

### *Crosstalk between cytokines signaling and EVs immunomodulation*

Breast cancer (BC) is the most common cancer in women, after skin cancer. Studies conducted in BC models have indicated that CCL5 is crucial in attracting TAMs to tumors (Walens et al. 2019). In a syngeneic 4T1 mouse model, antagonists of CCL5 suppressed TAM recruitment (Robinson et al. 2003). EVs from triple-negative breast cancer (TNBC) reprogrammed macrophage towards TAM with a pro-tumor phenotype through an indirect mechanism involving autocrine stimulation of tumor cells by CCL5. Tumor-educated macrophages promote TNBC through TLR2 and -3 signaling (Rabe et al. 2018). Accordingly, studies *in vitro* demonstrate that BC-derived exosomes stimulate the production of G-CSF, IL6, CCL2, and TNFα in macrophages, in a TLR2-dependent manner, inducing NF-kB activation (Chow et al. 2014). Additionally, both TNF-α and TLR2 were found to be required for

Lewis lung carcinoma metastasis, where the secreted factors from carcinoma cells induced macrophage production of TNF-α under versican stimulation through a process involving TLR2-TLR6 axis (Kim et al. 2009). Interestingly, Hartley et al. (2017) identified that bone marrow-derived monocytes exhibit increased PD-L1 expression when exposed to tumor-conditioned media. TNF-α was identified as a critical cytokine responsible for this upregulation. The TNF-α production by monocytes was stimulated through the activation of TLR2 in response to versican secreted by tumor cells (Hartley et al. 2017).

Tumor-derived EVs can modulate monocyte survival through antiapoptotic mechanisms and transport CD44v7/8 and CCR6 molecules that they take up (Baj-Krzyworzeka et al. 2006). CCL20, the ligand of CCR6, induces monocyte migration *in vitro* and triggers macrophage accumulation *in vivo* in a model of colon cancer (Nandi et al. 2016). High expression of CCL20 in tumor stroma has been identified as an adverse prognostic factor (Samaniego et al. 2018). Additionally, BC-derived exosomes promote monocyte survival due to the inhibition of caspase-8 activation through the MAPK pathway in monocytes (Song et al. 2016). Lysine demethylase 3B KDM6B (JDJM1A) is related to reduced TAMs (Osawa et al. 2013). Exosomal miR-138-5p produced by TNBC cells downregulates KDM6B expression in macrophages, regulating their polarization to an M2 phenotype and promoting the metastasis of BC to the lung (Xun et al. 2021).

The neuroblastoma (NBL) exosomes increased miR-21 and miR-155 in both M1- and M2-polarized cells, with concomitant downregulation of TERF1. This circuit was associated with chemotherapy resistance in NBL (Challagundla et al. 2015). Snail, an EMT transcriptional factor, directly activates the transcription of miR-21. The miR-21-containing exosomes were engulfed by CD14+ human monocytes, suppressing the expression of M1 markers and increasing M2 markers, leading to M2-like polarization of TAMs. Inhibition of miR-21 suppresses snail-induced M2-like macrophage polarization and tumor progression in animal models (Hsieh et al. 2018). Furthermore, melanoma-derived EVs containing miR-125b-5p have the potential to induce tumor-associated inflammation and angiogenesis as well as macrophage recruitment and survival, inducing the expression of IL1β, CCL1, CCL2, and CD80 in M1 macrophages by targeting Lysosomal Acid Lipase A (LIPA) (Gerloff et al. 2020).

While cytotoxic chemotherapy is known to be an effective treatment for invasive BC, there is evidence from experimental studies in mice suggesting that it may also have pro-metastatic effects. EVs released after chemotherapy contain high levels of annexin A6, a protein that promotes NF-κB-dependent activation of endothelial cells. This activation leads to the induction of CCL2, resulting in the expansion of $Ly6C^{+}CCR2^{+}$ monocytes in the pulmonary pre-metastatic niche, ultimately facilitating the establishment of lung metastasis (Keklikoglou et al. 2019). However, in a study by Plebanek and collaborators (2017), exosomes derived from non-metastatic melanoma cell lines migrate towards the lungs in tumor-bearing mice, preceding a significant increase in the $Ly6C^{low}$ subpopulation. Non-metastatic exosomes were enriched with PEDF, which promotes the differentiation of patrolling monocytes in macrophages, which polarize to an M1 profile associated with the killing and phagocytosis of melanoma cells. (Plebanek et al. 2017).

EVs carrying CSF-1 released by TNBC promote a tumor immune microenvironment associated with a better prognosis in TNBC patients through the induction of monocyte differentiation into macrophages; this leads to high levels of expression of CD163, MERKT, CD88, CD204, and

PD-L1. The TNBC EVs promote an interferon response in macrophages, with the expression of immunostimulatory genes associated with the M1 phenotype, such as *CXCL9* and *CXCL10* (Tkach et al. 2022). EVs present in the plasma of patients diagnosed with colorectal cancer are internalized by primary human monocytes cultured *in vitro* and lead to responses related to disease progression from a non-invasive state to an invasive state (Bjørnetrø et al. 2021). Results from a study conducted by Momen-Heravi and Bala (2018) suggest that EVs derived from head and neck squamous cell carcinoma (OSCC) are captured by monocytes and stimulate the activation of the NF-kB signaling pathway, which leads to an increase in MMP9 production and higher levels of COX2, PEG2 and VEGF mRNA after 24 hours of stimulation of THP-1 cells (Momen-Heravi & Bala 2018). Interestingly, this expression profile is also seen in TEMs recruited to TME via Ang-2, whose upregulation results from hypoxia, leading to the destabilization of blood vessels (Murdoch et al. 2007). In a VEGF-enriched TME, these blood vessels undergo angiogenic changes and sprout, ultimately forming new vasculature (Tait & Jones 2004).

In the TME, PKM2-containing ectosomes were found to accelerate the differentiation of monocytes into macrophages by activating glycolysis to provide acetyl-CoA, thus leading to the release of cytokines and chemokines promoting the progression of hepatocellular carcinoma (HCC). CCL1 was identified as one of the factors involved in a feedforward regulatory loop that further enhanced the excretion of PKM2 via ectosomes (Hou et al. 2020). PKM2, which catalyzes the final and irreversible step of glycolysis, is expressed at high levels in cancer cells. Studies have demonstrated that PKM2 promotes anabolic metabolism, cell survival, and tumor proliferation, mainly due to its intrinsic lower pyruvate kinase activity in the cytoplasm (Ward & Thompson 2012). HCC-derived exosomes upregulate the expression of PD-L1 through STAT3 signaling and increase the secretion of IL-6, IL-10, IL-1β, and TNF-α in macrophages both *in vitro* and *in vivo* (Cheng et al. 2017). IL-6/STAT3 signaling has been identified in numerous human cancers, including liver cancer, and is recognized as a crucial contributor to cancer initiation, growth, and advancement (Yu et al. 2007, 2009). Monocytes are reported to promote HCC growth via the IL-6/STAT3 axis, where the expression of STAT3 in these cells is correlated to a poor prognosis (Wu et al. 2011).

Chronic lymphocytic leukemia (CLL) is a type of cancer affecting mature B lymphocytes characterized by CD5+ and CD19+ cells (Nicholas et al. 2016). CCL-exosomes are reported to be enriched in Y RNAs that are uptaken by monocytes, leading to an upregulation of genes including *CCL2*, *CCL4*, *CCL5*, *CXCL9*, *CXCL10*, *CXCL11*, *IL6*, *PD-L1*, *IDO1*, and *PD-1* (Haderk et al. 2017). Y RNAs are conserved molecules (Perreault et al. 2007) that bind with proteins. The expression of Y RNA is altered in human tumors, including breast (Guo et al. 2018b), colon, liver, pancreatic (Meiri et al. 2010), and lung cancers (Li et al. 2018). In cultured monocytes/macrophages, Y RNAs play a role in caspase-dependent cell death and NF-κB-dependent inflammation via TLR7activation (Hizir et al. 2017).

Pancreatic cancer (PC)-derived exosomes downregulate HLA-DR expression on CD14+ monocytes, leading to tumor-induced immunosuppression in PC patients. Additionally, the exosomes can increase ROS production, arginase metabolism, and STAT3 signaling, leading to monocyte survival and immunosuppression (Javeed et al. 2017). Macrophages treated with PC cell-derived EVs and then co-culture with T cells arrest T cell function through the expression of T cell surface inhibitory receptors PD-1, TIGIT, and CTLA4, and

reducing the secretion of IL-2, IFN-γ, and TNF-α by these cells; this seems to occur through the transfer of miR-155-5p to macrophages, thus promoting their polarization to the M2 phenotype (Wang & Gao 2021). Maia et al. (2020) identified that PC-EVs mediate a pancreatic cancer-BM communication axis by reprogramming gene expression in BM CD11b+ cells. Additionally, they found downregulated genes linked to monocyte/macrophage activation and trafficking, including transcription factors associated with monocyte and macrophage differentiation, macrophage polarization, cell-cell communication, and chemotactic response, such as *Egr2*, *Nr4a1*, *Ccl2*, *Ccl3*, and *Rgs1* (Maia et al. 2020). PC-derived exosomes show significantly increased levels of the M2 markers CD163 and CD206 and induced an increased secretion of cytokines, including VEGF, MCP-1, IL-6, IL-1β, MMP-9, and TNFα in macrophages (Linton et al. 2018). Furthermore, exosomes from PC initiate the formation of a pre-metastatic niche in the liver by inducing fibronectin (FN) expression and the recruitment of macrophages through the transfer of macrophage migration inhibitory factor (MIF) from the exosomes to the liver (Costa-Silva et al. 2015).

IL-10, TGF-β2, and CCL22 production were significantly elevated in murine alveolar macrophages following exposure to exosomes from metastatic osteosarcoma cells. Also, CXCL9 and CXCL10, markers of the M1 phenotype, were decreased in these cells (Wolf-Dennen et al. 2020). Tumor-derived TGF-β-containing exomes induce the differentiation of myeloid cells with a decrease in CD14+ and HLA-DR expression and upregulate the secretion of IL-6, TNF-α, and TGF-β. When treated with these exosomes, monocytes significantly inhibited T-cell proliferation in a TGF-β-dependent manner (Valenti et al. 2006). In monocytes, EVs produced by osteosarcoma cells led to the upregulation of suppressive cytokines and effector molecules, such as IL-10 and arginase. Additionally, EVs caused a decrease in the expression of MHC class II and CD80 on monocytes, which was accompanied by an increase in the expression of PD-L1 on the monocyte membrane. (Luong et al. 2021). Tumor-derived exosomes containing PGE2 and TGF-β induce the accumulation of MDSCs in the tumor, increasing IL-6 and VEGF production, facilitating tumor growth and suppressing immune function (Xiang et al. 2009).

### *Effects of EVs from hypoxic tumors on monocytes and macrophages*

Studies have shown hypoxia as a significant driving force for tumor remodeling, promoting cancer progression and chemoresistance (Rohwer et al. 2009, Semenza 2010, Rofstad et al. 2010). Moreover, emerging evidence suggests a strong link between tumor hypoxia and immune suppression (Fu et al. 2021). Hypoxic lung-cancer-derived extracellular vesicles containing miRNA-103a from lung cancer cells can increase the expression of IL-10, CCL18, and VEGF-A in macrophages by directly targeting PTEN and causing activation of the PI3K/Akt and STAT3 signaling pathways. CD14+ monocytes with reduced expression of PTEN exhibited a CD163+CD206highHLA-DRlow phenotype (Hsu et al. 2018). Hypoxia-induced tumor exosomes are highly enriched in immunomodulatory proteins and chemokines, including CSF-1, CCL2, TGF-β, and FTH. They drive pro-tumoral M2-like macrophage polarization in vivo and in vitro. Also, exposure to tumor exosomes significantly decreased the expression levels of let-7a target genes such as IRS-1, IRS-2, INSR, and IGF1R in bone marrow-derived macrophages. These findings point to let-7a miRNA as a potential suppressor of the insulin-mediated mTOR signaling pathway in macrophages (Park et al. 2019). Hypoxic exosomes derived from ovarian

cancer cells increased the expression of M2 markers genes, CD206, arginase-1, and IL-10. These exosomes seem to deliver miR-21-3p, miR-125b-5p, and miR-181d-5p to macrophages, modulating the SOCS4/5/STAT3 pathway inducing M2 polarization that supports tumor progression and metastasis (Chen et al. 2018). Glioma exosomes derived from hypoxic tumors exert an immunosuppressive effect through the induction of MDSCs through miR-10a and miR-21, leading to the expression of TGF-β and IL-10; this probably occurs by targeting RORA and PTEN pathways in glioma-bearing mice (Guo et al. 2018a).

## Conclusion and future perspectives

As the frequency and occurrence of cancers continue to rise, there is an urgent demand for the creation of therapeutic approaches. This necessity arises as our comprehension of cancer's intricate nature as a disease evolves. Despite the significant biological functions that EVs play in both standard and pathological conditions and their capacity to better encompass the dynamic diversity of cancer, the limited understanding and technical obstacles have hindered their effective application in clinical settings. The functional relevance of human tumor-derived EVs' effects on monocytes and macrophages requires further characterization.

Future studies focusing on the production, composition, and physiology of different vesicles will add more knowledge about these, thus contributing to the development of possible therapeutic applications and a better understanding of tumor pathology, focused on understanding how the tumor microenvironment influences prognosis and development of the disease, allowing the development of engineered EVs based on these findings. Numerous preliminary investigations have unveiled EVs' as a diagnostic tool and their immunotherapeutic capabilities across diverse cancer types. However, clinical trials exploring the therapeutic aspects of engineered EVs are currently in their early stages of development. Furthermore, conducting pertinent clinical studies with a substantial sample size is desirable. Additionally, there is a need to enhance the standardized techniques for isolating and purifying EVs prior to their clinical implementation to better evaluate their effects on cells.

EVs in the extracellular environment play a crucial role in regulating monocyte and macrophage functions in the TME, significantly impacting cancer progression and immune evasion. The main related studies are summarized in Table I. Monocytes stimulated by EVs can migrate to cancer tissue, where they differentiate into TAMs or M2 macrophages, and produce several cytokines, such as IL-6, IL-1β, TNF-α, and IL-10, enhance the membrane expression of PD-L1, CD14 e CD206, exhibiting a pro-tumoral profile and supporting tumor growth (Figure 1). Therefore, EVs can modulate the immune response and promote tumor progression by altering the phenotype and function of these cells. Overall, EVs provide insights into the complex interplay between cancer cells and the immune system.

**Table I. Main findings of the effects of extracellular vesicles on monocytes, macrophages, and MDSC cells related to the immunomodulation of functions and phenotypes.**

| Tumor | Modulation | Action on | Study type | Ref |
|---|---|---|---|---|
| Squamous head and lung cancer | Induced secretion of TNFα and IL-1β | Monocytes | In vitro | (Gärtner et al. 2018) |
| Colorectal cancer | Increased CD14+ in M0 and HLA-DR in M1 and M2 macrophages | Macrophages | In vitro | (Popěna et al. 2018) |
| | Upregulation of PD-L1 | CD206+ TAMs | In vitro | (Yin et al. 2022) |
| Breast cancer | Upregulation of PD-L1 | Macrophages | In vivo and in vitro | (Yao et al. 2020) |
| | Production of G-CSF, IL6, CCL2, and TNFα | Macrophages | In vivo and in vitro | (Chow et al. 2014) |
| | Decreased expression of KDM6B and M2 polarization | Macrophages | In vivo and in vitro | (Xun et al. 2021) |
| | Increased expression of CD163, MERKT, CD88, CD204, and PD-L1 | Macrophages | In vitro | (Tkach et al. 2022) |
| Glioblastoma | Increased expression of arginase-1, IL-10, and CD206 | Macrophages | In vitro | (Azambuja et al. 2020) |
| Gastric cancer | Increased expression of CD206, IL-10, and CCL1 | PD1+ Macrophages | In vitro | (Wang et al. 2018) |
| Melanoma | Decreased HLA-DR expression and increased IL-6 and CCL2 | M-MDSC | In vivo and in vitro | (Huber et al. 2018) |
| | Increased PD-L1, IL-1β, IL-6, IL-10, TNF-α, and COX-2 | M-MDSC | In vivo and in vitro | (Fleming et al. 2019) |
| | Increased expression of IL1β, CCL1, CCL2, and CD80 | M1 macrophages | In vitro | (Gerloff et al. 2020) |
| Renal cancer | Production of ROS and NO, secretion of IL-10 and TGF-β and arginase activity | M-MDSC | In vivo and in vitro | (Gao et al. 2020) |
| Head and neck squamous cell carcinoma | Activation of the NF-kB pathway increased iMMP9 production and expression of COX2, PEG2, and VEGF | Monocytes | In vitro | (Momen-Heravi & Bala 2018) |
| Hepatocellular carcinoma | Increased expression of PD-L1 and increased secretion of IL-6, IL-10, IL-1β, and TNF-α | Macrophages | In vitro and in vivo | (Cheng et al. 2017) |
| Pancreatic cancer | Arrest T cell and increased expression of PD-1, TIGIT, and CTLA4 | Macrophages | In vitro | (Wang & Gao 2021) |
| | Increased secretion VEGF, MCP-1, IL-6, IL-1β, MMP-9, and TNFα | Macrophages | In vitro | (Linton et al. 2018) |
| Lung cancer | Increased expression of IL-10, CCL18, and VEGF-A | Macrophages | In vitro | (Hsu et al. 2018) |
| Ovarian cancer | Increased expression of CD206, IL-10 and arginase-1 | Macrophages | In vitro | (Chen et al. 2018) |
| Glioma | Increased expression of TGF-β and IL-10 | MDSCs | In vitro | (Guo et al. 2018a) |

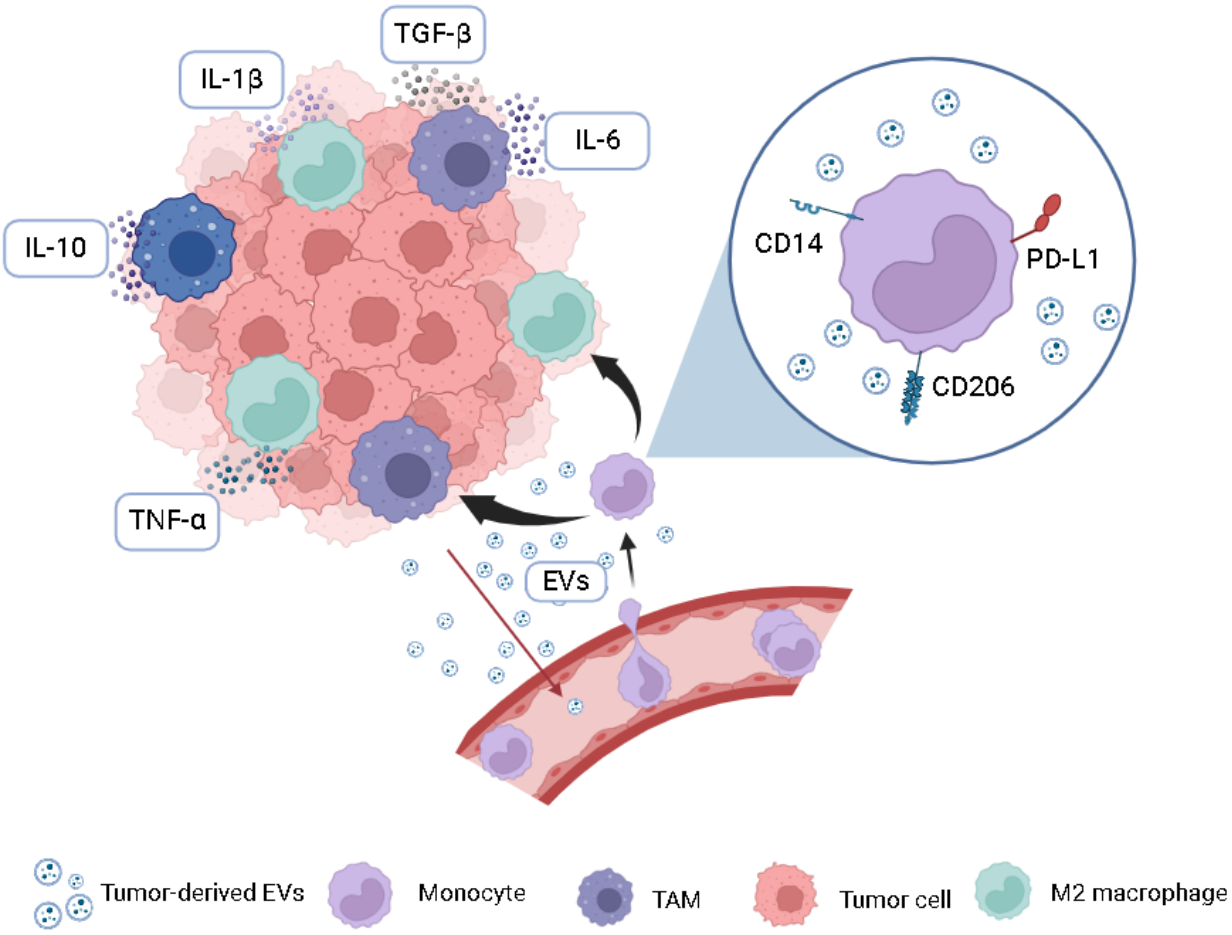


**Figure 1. Tumor-derived extracellular vesicles affect the function and phenotype of monocytes. The release of EVs under different conditions can induce monocyte differentiation into macrophages, which are polarized towards a profile that supports tumor growth and progression. This process also leads to the upregulation of the main cytokines and chemokines released by monocytes within the TME, such as IL-6, VEGF, TNF-α, and IL-10. Moreover, EVs upregulate CD14, PD-L1, and CD206 expression on monocytes, thus preventing apoptosis and enhancing their migration.**

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Almeida PP conceived the idea; Almeida PP and Renovato-Martins M wrote the manuscript; Moraes JA, Renovato-Martins M, and Barja-Fidalgo C revised the manuscript. All authors approved the final version.