Introduction
As cancer represents a very diverse biology depending on the genetic background, the organ of origin and confounding factors it remains ambitious to dissect this complex cellular microenvironment into its main driving factors. Among these factors an important role has been attributed to both the adaptive and innate immunity. For a long time, the immune regulatory capacity (e.g. regulatory T cells) of the adaptive immune system was a major focus of research concerning the involvement of immune cells in the tumor microenvironment with only few reports published on its role in tumor growth promotion and metastasis.

In contrast terms such as angiogenesis, tumor growth or metastasis have been attributed to cells of innate immune origin (Hicks et al., 2006). The innate immune system is represented by different cell subsets including natural killer (NK) cells, dendritic cells (DC), neutrophils, and macrophages (MΦ). Tumor-associated macrophages (TAMs) constitute a major part of the leukocytic infiltrate in human cancer and the amount of tumor infiltrating macrophages has early been associated with clinical outcome (Mantovani et al., 2008; Pollard, 2009). When assessing studies that identified TAMs simply as CD68+ cells it is challenging to assign a strict pro- or anti-tumorous function to the TAM infiltrate. Nevertheless, macrophage infiltration is associated with poor prognosis in breast cancer (Finak et al., 2008; Beck et al., 2009), Hodgkin's lymphoma (Steidl et al., 2010), T-cell lymphoma (Niino et al., 2010), cervical cancer (Steidl et al., 2010; Lenz et al., 2008; Hammes et al., 2007; Zhang et al., 2011c; Kamper et al., 2011) and uveal melanoma (Bronkhorst et al., 2011). In contrast, it has been linked with a favorable prognosis in colorectal and gastric cancer (Forssell et al., 2007; Sconocchia et al., 2011; Ohno et al., 2003). Interestingly, several studies now confirm that the location of TAMs in the tumor microenvironment and in regard to tumor cells seems to influence their prognostic role (Ohno et al., 2003; Allavena and Mantovani, 2012). In colon cancer for example, higher macrophage infiltration at the invasive front of the tumor is associated with both an improvement of overall survival and reduced hepatic metastasis (Zhou et al., 2010). The classical six hallmarks of cancer are cell growth, ignoring growth-inhibition, the avoidance of cell death, replication without limitation, sustained angiogenesis and invasion through basement membranes into circulation (Hanahan and Weinberg, 2000). Growing knowledge on the biology of cancer stresses the role of the immune system, in particular macrophages, on several aspects of tumor biology. It more and more becomes clear that beside the classical six hallmarks, novel hallmarks of cancer can be assigned to cells of the microenvironment. Tumor-associated macrophages as part of the tumor microenvironment are involved in novel hallmarks of cancer such as tumor-promoting inflammation and avoidance of immune destruction. Moreover, they are actively involved in all classical six hallmarks by exerting TAM-specific tumor-sustaining properties discussed below (Hanahan and Weinberg, 2000; Hanahan and Weinberg, 2011).
Origin and activation status of macrophages

Macrophages are in general believed to arise from circulating monocytes that emigrate from blood vessels and differentiate into macrophages in the peripheral tissue. A variety of tissue associated macrophages exist that exert an important role in tissue homeostasis. Under homeostatic conditions, tissue macrophages comprise langerhans cells in the epidermis, osteoclast's in the bone, alveolar macrophages in the lung, red-pulp, white-pulp, marginal-zone and metallophilic macrophages in the spleen, kuffer cells in the liver and microglial cells in the central nervous system (Gordon and Taylor, 2005). In general tissue macrophages are believed to exhibit an intrinsic anti-inflammatory phenotype under homeostatic conditions (Murray and Wynn, 2011).

Macrophages are subject to a variety of concurrent stimuli in vivo. In vitro, macrophages can be polarized by single agent stimulation into rather pro- or anti-inflammatory macrophages. According to the stimulus, macrophages are divided into a simplified M1-like and M2-like phenotype classification analogue to the Th1-Th2 dichotomy in T cell biology (Biswas and Mantovani, 2010). The pro-inflammatory "classically activated" M1-like phenotype can be induced by inflammatory signals such as interferon, LPS and other bacterial stimuli and mediates defense against bacteria, protozoa and viruses (Murray and Wynn, 2011). The "alternatively activated" M2-like phenotype is induced by IL4 or IL-13 ("M2a"), LPS or immune complexes ("M2b"), IL-10 ("M2c") and is associated with wound healing and tissue repair (Gordon, 2003; Gordon and Martinez, 2010). As there exist more stimuli than those mentioned, consecutively a plethora of other macrophage phenotypes have been described both in vivo and in vitro. Whereas they often share some features with M1-like or M2-like macrophages they mostly exhibit their own unique set of immunomodulatory capabilities.

Current concepts of tumor associated macrophages

Macrophages play a prominent role in the stromal and leukocyte compartment in malignancy and distinct macrophage subsets in cancer have been described (Mantovani et al., 2008; Pollard, 2009; Grivennikov et al., 2010; Mantovani et al., 2010a). As macrophages in human cancer can neither be classified into classical activated M1-like or alternatively activated M2-like macrophages they are termed tumor-associated macrophages (TAMs). Macrophages represent a cell type with an extreme functional plasticity enabling them to integrate and respond to different stimuli (Stout et al., 2009). Despite profound functional differences between human and murine macrophages, most functional properties of TAM subtypes have been studied in murine cancer models due to the difficulty to molecularly characterize small numbers of macrophages from human tumor specimens (Clark et al., 2007).

Mechanisms of macrophage recruitment and macrophage polarization

Macrophages are among the first immune cells to infiltrate already preinvasive tumorous lesions and persist during the development into invasive cancer (Clark et al., 2007). Cancer is associated with inflammation that results in recruitment of bone marrow derived cells (Hanahan and Weinberg, 2011; Coussens and Werb, 2002). Growth factors like CSF-1 (colony stimulating factor 1) and vascular epithelial growth factor (VEGF), but also monocyte chemotactic protein-1 (MCP-1) as well as several CCL chemokines and other molecules have been shown to induce chemotaxis of monocytes into the tumor environment (Lewis and Pollard, 2006). In an elegant study in three different murine tumor models (the BALB/c 4T1 mammary tumor model, the BALB/c mammary adenocarcinoma TS/A model and the C57BL/6 3LL lung carcinoma model) the inflammatory Ly6C+ monocyte subset was shown to be the major monocyte subset to localize into the tumor and to give rise to TAM subsets in the tumor (Movahedi et al., 2010). With respect to the specific tumor, the molecules are secreted by tumor cells themselves or adjacent stromal cells. In skin carcinogenesis for example carcinogen application induces proliferation of fibroblasts that secrete MCP-1 which results in chemotaxis of macrophages. Neutralization of MCP-1 almost completely blocks this accumulation of macrophages in the tumor (Zhang et al., 2011a). VEGF, beside its strong angiogenic role, recruits monocytes into the tumor microenvironment and blockade of VEGF by bevacizumab results not only in reduced vessel density, but also in reduced TAM infiltration (Roland et al., 2009).

Once migrated to the tumor site monocytes differentiate into macrophages under the influence of macrophage colony-stimulating factor (M-CSF). Further tumor cell-derived factors drive macrophage polarization into one of the TAM subpopulations described below. In general the induction of a TAM related phenotype has been brought in context with tumor cell derived mediators such as M-CSF (Duluc et al., 2007), IL-4, IL-10, IL-6 (Duluc et al., 2007; Song et al., 2009), transforming growth factor β (TGF-β1), prostaglandin E2 (PGE2) (Lewis and Pollard, 2006; Heusinkveld et al., 2011), hyaluron fragments (Kuang et al., 2007) and the leukemia inhibitory factor (LIF) (Duluc et al., 2007). In cervical cancer, monocytes are skewed from a DC towards a macrophage phenotype by the production of PGE2 and IL-6 from tumor cells (Heusinkveld et al., 2011; Kim et al., 2011).

As stated above, the terms "classically activated" and "alternatively activated wound healing" are counterintuitive in the description of tumor-associated...
macrophages as the conditions that dominate the tumor microenvironment are rarely the same as in infection (exceptions might be true for infectious related cancers such as cervical cancer and vulvar cancer). Despite this statement researchers attempt to classify tumor-associated macrophages into the M1-like/M2-like terminology as of similarities in expressed marker profiles. It is yet unclear whether similarities between certain tumor-associated macrophages and the M1-like or M2-like macrophages are due to the different types of tumors that were investigated, as proposed by some researchers, or whether there might be a "M1-like/M2-like switch" during tumor progression. Despite the vast majority of reports describing TAM phenotypes that share properties with M2 macrophages, TAM with expression of both M2-like and M1-like markers have been described as well (Biswas et al., 2006). These TAMs show high expression of genes encoding immunosuppressive cytokines (II10, Tgfb1), phagocytosis-related receptors/molecules (Msr2, C1q) and inflammatory chemokines (Ccl2, Ccl5) as well as IFN-inducible chemokines (Cxcl9, Cxcl10, Cxcl16) (Biswas et al., 2006). Others have shown mixed M1-like (CD14^+HLA-DR^+) and M2-like (CD14^CD163^+) TAM infiltration (Buddingh et al., 2011). These TAMs are sarcoma associated, but similar results exist for carcinoma as well (Movahedi et al., 2010). Conversely TAMs in cutaneous squamous cell carcinoma partially express the M2-like markers CD209 and CCL18, others express M1-like markers STAT1, IL-23, IL-12 and CD127 and again others express markers of both M1-like and M2-like macrophages (Pettersen et al., 2011). In other carcinomas there are TAMs with a predominantly M2-like marker expression status (Ma et al., 2010). Typical genes that are expressed by TAMs include IL-1, IL-6 and tumor necrosis factor a (TNF-a) (Lewis and Pollard, 2006). In consequence, TAMs are often termed M2-like macrophages by many researchers despite their integration of probably much more diverse stimuli than only IL-4 and/or M-CSF which suggests that a much more dynamic model of macrophage activation in tumor immunology must be found to usefully characterize TAMs (Pettersen et al., 2011). Independent from the assignment to the M1-like or M2-like macrophage class, the underlying intracellular pathways that are activated in TAM are far from understood. Several pathways have been shown to be important for specific functions of TAMs, for example an Ets2-driven transcriptional program as well as a Wnt-signaling program have been associated with invasion and metastasis in murine breast cancer associated TAMs (Zabuwalawala et al., 2010; Ojalvo et al., 2010).

Consequently, additional TAM subpopulations will likely be identified with specialized tumor-associated properties that can be allocated functionally to cancer specific needs such as growth, invasion, angiogenesis and metastasis.

Pro-inflammatory and growth promoting properties of TAMs

Tumor-promoting inflammation and avoidance of immune destruction represent novel hallmarks of cancer (Hanahan and Weinberg, 2011). Macrophages have been shown to support tumor cell growth by the activation of different pathways. Several soluble growth factors, eg. IL-1, IL-6, TNF-α, TGF-β, epidermal growth factor (EGF), platelet-derived growth factor (PDGF) produced by macrophages have been indicated to be involved in tumor cell growth, (Lewis and Pollard, 2006). TNFu is produced by tumor cells and by inflammatory cells in chronic inflammation. It promotes cell survival by induction of anti-apoptotic molecules via TNFR1 and TNFR2 (Lin and Karin, 2007). EGF plays an important role in murine breast cancer (Joyce and Pollard, 2009). TAMs are major producers of EGF, and there exists interplay between EGF producing TAMs and EGFR expressing tumor cells, which reciprocally produce M-CSF to support macrophage survival and EGF production. Another important activating pathway in TAMs is mediated by signal transducer and activator of transcription 3 (STAT3) known to result in IL-6 expression. This pro-inflammatory cytokine is known to induce proliferation of malignant cells (Lin and Karin, 2007; Grivennikov et al., 2009; Bromberg and Wang, 2009) and IL-6 has been found to have a pivotal role in Kaposi sarcoma, multiple myeloma, Hodgkin lymphoma, breast cancer, ovarian cancer and others (Osborne et al., 1999; Bommert et al., 2006; Cozen et al., 2004; Berger, 2004; Stone et al., 2012). Opposing roles have been attributed to TGF-β.

Whereas TGF-β might inhibit tumor growth by reducing IL-6 secretion (Lin and Karin, 2007; Derynck et al., 2001), enhanced TGF-β secretion is often observed in carcinoma and is associated with enhanced epithelial-mesenchymal transition (EMT). EMT results in higher invasiveness of epithelial tumor cells and metastasis due to changed expression levels of adhesion molecules and metalloproteinases (Derynck et al., 2001). TGF-β production by tumor cells also induces IRAK-M (Interleukin-1 receptor-associated kinase) a negative regulator of Toll-like receptor signaling in TAM, which is part of the immunosuppressive phenotype of TAM (Standiford et al., 2011).

Immunosuppressive properties of TAMs

Immunosuppressive functions of TAMs seem to be contradictory to the strong inflammatory tumor-microenvironment and the inflammatory properties of macrophages. Although TAMs produce several chemokines that are associated with inflammation in immunity against pathogens, under sterile inflammatory conditions in cancer these molecules rather exert a growth promoting influence on tumor cells. TAMs are poor producers of IL-12 but produce...
IL-10 and TGFβ (Sica et al., 2000). This effect might be due to STAT3 activation in TAMs opposing STAT1 driven Th-1 anti-tumor responses (Allavena and Mantovani, 2012; Yu et al., 2009). Expression of MHC class II molecules on TAMs is actively downregulated by tumor cell derived TGF-β1, IL-10 and PGE₂ (Lewis and Pollard, 2006).

Direct inhibition of immune responses by TAMs has been described as well (Kryczek et al., 2006). IL-10 and TNF-α in the tumor milieu induce expression of PD-L1 (also termed B7-H1) on the membrane of tumor-associated macrophages. Although naïve T cells can be stimulated via PD-L1, its most prominent role is the inhibition of activated effector T cells through the PD-1 receptor (Kuang et al., 2009).

Allavena and Mantovani reported an additional - indirect - mechanism of creating an anti-inflammatory tumor milieu, namely the recruitment of other non-inflammatory immune cells into the tumor microenvironment (Allavena and Mantovani, 2012). In this context, CCL17 and CCL22 produced by TAMs have been implicated to predominantly attract Th2 and Tregs that are non-cytotoxic cells (Allavena and Mantovani, 2012; Mantovani et al., 2010b). Macrophage-derived CCL18 recruits rather naïve T cells that are primed under immune regulatory conditions (Schuttyser et al., 2002). In a murine model of colorectal cancer, F4/80⁺ TAMs were found to secrete large amounts of CCL20 attracting CCR6⁺ Treg cells to the tumor side (Liu et al., 2011).

**Invasion and metastasis promoting properties of TAMs**

Several macrophage-associated mechanisms in the tumor microenvironment exist that support invasion and metastasis of tumor cells. An invariant property of tissue macrophages is the production of matrix metalloproteinases, cathepsins and other proteolytic enzymes that degrade the extracellular matrix (Vasiljeva et al., 2006; Hagemann et al., 2004). While useful in wound healing this macrophage function subsequently allows tumor cells to invade and spread locally. Invasion is a prerequisite for metastasis as one of the major hallmarks of malignancy. As shown in the PyMT mouse tumor model, the property of tumor cells to invade tissues is dependent on macrophages (Goswami et al., 2005; Wyckoff et al., 2004). By producing CSF-1 and TNF-α, tumor cells recruit macrophages which produce metalloproteinases 2, 3, 7, and 9. Invasion of tumor cells is prominently accompanied by coordinated migration of macrophages (Goswami et al., 2005; Wyckoff et al., 2004). Intravital imaging has provided direct evidence that perivascular macrophages in mammary tumors are involved in the intravasation of cancer cells (Wyckoff et al., 2007). Moreover, either inhibition of EGF signaling or deletion of macrophages can reduce the number of tumor cells that enter the blood stream (Lewis and Pollard, 2006). Further molecular investigations revealed that especially invasive TAMs are a unique subpopulation of TAMs exhibiting increased WNT signaling and promoting carcinoma cell motility (Ojalvo et al., 2010).

Whereas the CSF-1/EGF signaling axis seems to promote invasiveness in certain cancer models, in others an important role in invasiveness has been attributed to EMT (Thiery, 2002). Expression of mesenchymal markers is correlated with TAM infiltration in a F9-teratocarcinoma model and depletion of macrophages results in a decrease of mesenchymal associated genes (Bonde et al., 2012). Moreover, growth of tumor cells in macrophage-conditioned media results in EMT and enhanced invasiveness. EMT can be induced in cancer cells in vitro by addition of TGF-β to the cell culture and experimental data suggest that TGF-β is also the driving force of macrophage-induced EMT in vivo (Derynick et al., 2001; Bonde et al., 2012).

**Lymphangiogenesis promoting properties of TAMs**

Depending on the tumor characteristics tumors show either a lymphatic or a haematogenic metastasis pattern. Degree of lymphangiogenesis predicts poor clinical prognosis in most malignant diseases. Tumor cells themselves show considerable production of lymphangiopoietic vascular endothelial growth factors (VEGF)-C and -D. In addition, macrophages can produce high amounts of VEGF-C and VEGF-D and macrophage infiltration is associated with peritumoral lymphangiogenesis in lung adenocarcinoma and cervical cancer (Zhang et al., 2011b; Utrera-Barillas et al., 2010). Schoppmann et al. identified a subset of VEGFR-3⁺ tumor-associated macrophages that stains for VEGF-C- and VEGF-D in human cancer probably being the main producers of these lymphangiopoietic factors (Schoppmann et al., 2002; Schoppmann et al., 2006). In SCC, VEGF-C expression is associated with CD68⁺ CD163⁺ TAMs, whereas other immune cells infiltrating the tumor such as CD3⁺ T cells or CD11c⁺ DC do not express this lymphangiogenesis marker (Moussai et al., 2011). In line with this, inhibition of VEGFR-3 signaling suppresses lymphangiogenesis in cancer and metastasis to regional lymph nodes (He et al., 2002). Moreover in mice models of inflammation-induced lymphangiogenesis, macrophages were found to form lymphatic-like tubes in vitro. Moreover they showed the ability to assemble into lymphatic vessels that arose de novo and expressed classical lymphatic endothelial markers such as LYVE-1, VEGFR-3, podoplanin and Prox-1 (Maruyama et al., 2005).

**Angiogenesis promoting properties of TAMs**

Cancer requires angiogenesis beyond a tumor size of a few millimeters. Hypoxic conditions in immunity against pathogens are frequent and macrophages have adapted to this condition by a specific genetic program under the control of the transcription factor family
hypoxia-inducible factor HIF (Leek et al., 2002). Cancer angiogenesis is not dependent on one mechanism, but several pathways have been described. The neoangiogenesis in cancer development is known as "angiogenic switch". In general cancer cells have been shown to induce this angiogenic switch by production of angiogenic factors the most prominent being VEGF. Nevertheless angiogenesis is positively correlated with macrophage infiltration in various studies suggesting a possible role for this cell subset in angiogenesis (Rogers and Holen, 2011; Murdoch et al., 2008; Clear et al., 2010). In macrophages HIF-1 is induced under hypoxic conditions in the tumor microenvironment resulting in the production of pro-angiogenic molecules. Several macrophage derived molecules that are directly angiogenic (among those are VEGF, TNF-α, IL-8, CXCL8 and bFGF) and others that modulate angiogenesis (e.g. MMP2, MMP-7, MMP-9, MMP-12, COX-2) have been described (Lewis and Pollard, 2006). The most well-known element is VEGF that is produced by a specialized subset of TAMs in hypoxic areas of breast cancer (Lewis and Pollard, 2006). In murine tumor models these VEGF-producing cells can be identified by Tie-2 expression (De Palma et al., 2005). Mechanisms of modulation of angiogenesis other than VEGF comprise the Wnt-pathway dependent production of Flt1, an inhibitor of angiogenesis, in myeloid cells (Stefater et al., 2011), neurotrophin 5, FGF13, PDGFRα and Bv8 (Shojaei et al., 2007a; Shojaei et al., 2007b, Dong et al., 2004). Experimental mouse models using clodrolip depletion of TAMs have shown that macrophage depletion results in drastic reduction of vessel density and decrease in tumor growth (Zeisberger et al., 2006).

Future concepts of tumor associated macrophages (TAM)
The Role of TAMs in Chemotherapy Resistance
Most of the functions that are attributed to TAMs are pro-tumoral, e.g. tumor progression, vascularization, invasion and metastasis. Cell death of cancer cells upon exposure to chemotherapy can occur in an immunogenic or a non-immunogenic way, in the past thought to be represented by necrosis and apoptosis, respectively (Zitvogel et al., 2008). New data suggest that this dichotomy is an oversimplification as necrosis can induce local immunosuppression as well as certain types of apoptosis are immunogenic which has been shown to be related to translocation of calreticulin to the cell surface (Vakkila and Lotze, 2004; Casares et al., 2005; Obeid et al., 2007). Immunogenic tumor cell death is thought to be a prerequisite for a contribution of the immune system to the eradication of cancer cells, called "bystander effect" (Zitvogel et al., 2006; Lake and van der Most, 2006). In the past, this effect has mainly been attributed to dendritic cells and T cells.
Similar effects could be observed by stimulating M2-costimulatory molecules and production of IL-12. Into M1-like macrophages with induction of Th1 cells results in a repolarization of M2-like microenvironment (Heusinkveld et al., 2011). The plastic nature of macrophages allows to re-polarize them into a more tumoricidal phenotype than the tumor associated phenotype, for example the pro-inflammatory M1-like phenotype. Reversion of the tumor-associated M2-like status into a M1-like phenotype has been shown to improve anti-tumor responses. Especially IFNg, nitric oxide and IL-12 produced by macrophages or expressed exogenously repress tumor cell growth (Lewis and Pollard, 2006; Peron et al., 2004). In general, this can be accomplished by different methods. A combination of chemotherapy with vincristine, cyclophosphamide and doxorubicin together with immunotherapy with CpG-ODN led to a shift in the TAM population from a rather M2-like towards a M1-like phenotype with upregulation of MHC II, IFN-γ, TNF-α and IL-12 (Buhtoiaarov et al., 2011). Zoledronic acid, besides its macrophage depleting effect, has been shown to reduce VEGF expression in TAMs as well as to induce expression of iNOS, one of the hallmark genes of M1-like polarization (Coscia et al., 2010). The histidine-rich glycoprotein (HRG) skews TAM polarization away from the M2-like to a M1-like phenotype and suppresses placental like growth factor (PLGF) (Rolny et al., 2011; Huang et al., 2011). Inhibition of PGE2 production in tumor cells by COX inhibitors and blocking of IL-6 can prevent differentiation of monocytes into M2-like macrophages in the tumor microenvironment (Heusinkveld et al., 2011). Interaction of already polarized M2-like macrophages with Th1 cells results in a repolarization of M2-like into M1-like macrophages with induction of costimulatory molecules and production of IL-12. Similar effects could be observed by stimulating M2-like cells with CD40L+ cells and IFN-γ (Heusinkveld et al., 2011).

**Therapeutic depletion of TAMs**

TAM infiltration in tumors is associated with bad prognosis and besides repolarization of macrophages, therapeutic depletion might be an attractive approach against invasion, angiogenesis, tumor growth and metastasis as well. For depletion of macrophages, clodronate-encapsulated liposomes are most often used in the experimental murine setting. Depletion of TAMs by this method in mouse models has been shown to significantly inhibit tumor growth (Zeisberger et al., 2006).

Moreover, recent studies suggest that medications with proven clinical benefit exert part of their action through inhibition or depletion of macrophages. Bisphosphonates are mainly used to treat osteoporosis and have been shown to lower the incidence of bone metastases in multiple myeloma, breast and prostate cancer (Rogers and Holen, 2011). Bisphosphonates mainly affect osteoclasts, but macrophages that arise from the same precursors are affected as well. In macroprhages bisphosphonates induce apoptosis in vitro and inhibit M-CSF induced proliferation (Rogers and Holen, 2011). Moreover, in murine models, the bisphosphonate zoledronic acid decreased macrophage infiltration into the tumor, VEGF expression and macrophage associated MMP-9 expression (Giraud et al., 2004; Tsagozis et al., 2008).

Depletion of macrophages was shown to decrease tumor growth in various murine cancer models: in murine lung cancer, depletion of macrophages results in a reduction of macrophage infiltration with reduction of bone metastasis; in murine breast cancer, macrophage infiltration and neo-vascularization is impaired and a shift from M2-like to M1-like phenotype is observed; in teratocarcinoma and rhabdomyosarcoma, depletion of macrophages results in reduction of tumor volume and reduction of blood vessel density, respectively (Rogers and Holen, 2011). Moreover, depletion of macrophages has been shown to increase response to chemotherapy, for example sorafenib in a murine model of metastatic liver cancer. In this model, sorafenib induced macrophage recruitment is inhibited by concomitant application of zoledronic acid and results in decreased tumor angiogenesis and lung metastasis (Zhang et al., 2010). Consequently, the development of effective strategies against cancer might target not only the cancer cell, but also other players in the tumor microenvironment, among which the tumor-associated macrophage plays a prominent role.

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