Tumor associated macrophages and neutrophils in cancer

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ABSTRACT

The tumor microenvironment is a complex framework, in which myeloid cells play important roles in sculpting cancer development from tumor initiation to metastasis. Immune cells are key participants of the tumor microenvironment where they can promote or inhibit cancer formation and development. Plasticity is a widely accepted hallmark of myeloid cells and in particular of the monocyte–macrophage lineage. It includes the ability to display a wide spectrum of activation states in response to distinct signals and classical M1 or alternative M2 macrophages represent a paradigm of this feature. Neutrophils have long been viewed as terminally differentiated effector cells, playing a major role during the acute phase of inflammation and resistance against microbes. Recent evidence questioned this limited point of view, indicating that neutrophils can interact with distinct cell populations and produce a wide number of cytokines and effector molecules. Therefore, macrophages and neutrophils are both integrated in the regulation of the innate and adaptive immune responses in various inflammatory situations, including cancer.

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Introduction

The tumor microenvironment, characterized by a chronic inflammation and consisting of various host components including stromal cells, growing blood vessels and inflammatory infiltrate, is known to play important roles in cancer development and behavior (Allavena et al. 2008; Coussens and Werb 2002; Hanahan and Weinberg 2011). A wide spectrum of leukocytes takes part in the tumor microenvironment and may exert a dual role on tumor development and progression. Indeed, immune cells can directly eliminate the tumor cells or participate in the induction of an anti-tumoral immune response but can also be recruited and appropriately trained by tumor cells to favor the tumor growth and progression. This immune cell infiltrate consists of many players, including macrophages and neutrophils.

Tumor-associated macrophages (TAM) are a well-known component of the inflammatory infiltrate of several tumors and key producers of many mediators (e.g. chemokines), which take part in the activation and maintenance of the chronic inflammatory process (Mantovani et al. 1992).

Neutrophils are the predominant leukocyte subset in human peripheral blood, with a well-established role in the first line of defence against microbial pathogens. Because of their short life span and fully differentiated phenotype, their role in cancer-related inflammation has long been considered negligible. In analogy with macrophages, tumor-associated neutrophils (TAN) can exert pro-tumoral as well as anti-tumoral functions and evidence derived from animal models has suggested that neutrophils can be polarized toward distinct phenotypes in response to distinct tumor-derived signals (Fridlender et al. 2009; Mantovani 2009; Mantovani et al. 2011).

In addition to macrophages and neutrophils, cancer growth is accompanied by the expansion of a heterogeneous population of immunosuppressive cells functionally defined as myeloid-derived suppressor cells (MDSC) (Gabrilovich et al. 2007; Peranzoni et al. 2010). In mice, they are classically divided in monocytic CD11b+Ly6C+ MDSC (Mo-MDSC) and granulocytic CD11b+Ly6G+ MDSC (G-MDSC). However, the distinction between the monocytic and granulocytic MDSC subsets should not be considered strictly since a large proportion of M-MDSC can acquire phenotypic, morphological and functional features of G-MDSC after a transcriptional...
epigenetic silencing of the retinoblastoma gene (Youn et al. 2013). These myeloid cells share functional and phenotypic similarities with TAM and TAN, but this relationship needs to be further investigated (specially in humans) and is beyond the scope of this review.

The pro-tumoral activities of TAM and TAN include functional mechanisms involved in the extracellular matrix (ECM) remodeling, enhancement of cancer cell invasion and metastasis, angiogenesis, cancer cell proliferation, lymphangiogenesis and in the inhibition of the anti-tumoral immune surveillance (Mantovani et al. 2008, 2011; Qian and Pollard 2010). In contrast, TAM and TAN can exert anti-tumoral activities through a direct cytotoxic activity against tumor cells as well as through the release of a wide range of mediators (e.g. cytokines, chemokines and growth factors) able to recruit and activate a number of cells of both the innate and adaptive immune systems (Mantovani et al. 2002; Tecchio et al. 2013).

It is the purpose of this review to explore the immunobiology of TAM and TAN, with a particular attention given to their recruitment and polarization in cancer, their roles in tumor growth and progression and their significance in clinical settings.

**Recruitment of leukocytes to the tumor site**

Stromal and tumor cells produce a wide spectrum of chemokines and growth factors able to recruit circulating monocytes and differentiate them into macrophages. For instance, CCL5/RANTES, CXCL12/SDF-1 and CXCL1/fraktalkine were found in neoplastic tissues and contribute to macrophage recruitment and tumor promotion (Ballwill 2004; Bottazzi et al. 1983; Mantovani et al. 2004; Reed et al. 2012; Ueno et al. 2000). Moreover, in addition to chemokines, growth factors and non-canonical chemotactic peptides, such as vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-β), basic fibroblast growth factor (bFGF), macrophage colony stimulating factor (M-CSF/CSF-1), urokinase plasminogen activator (uPA) and the antimicrobial peptide β-defensin-3, have been involved in monocyte recruitment and macrophage differentiation (Allavena and Mantovani 2012; Bierie and Moses 2010; Jin et al. 2010; Lin et al. 2002; Linde et al. 2012; Reed et al. 2012; Zhang et al. 2011). The tumor-associated inflammation triggers also the production of CXC chemokines (CXCL8, CXCL1, CXCL2, CXCL3, CXCL5), known for their role in neutrophil recruitment in both physiological and pathological conditions and involved in cancer progression, favoring tumor angiogenesis and metastasis (Keeley et al. 2010; Lazennec and Richmond 2010; Mantovani et al. 2011). Accordingly, in a tumor graft model, CXCL17, the latest identified member of the CXC family, promoted the tumor growth associated with the recruitment of immature myeloid derived CD11b+Gr1+ F4/80+ cells in the tumor (Matsu et al. 2012). In addition, in murine models of inflammation-induced skin tumors and intestinal colitis-associated or spontaneous cancer, myeloid cells infiltrated tumors and CXCR2 deficiency or neutrophil depletion suppressed inflammation-related tumorigenesis and the onset of spontaneous tumors (Jamieson et al. 2012). Interestingly, epithelial barrier deterioration induced by colorectal-cancer initiating genetic lesions (i.e. loss of the adenomatous polyposis coli tumor suppressor) resulted in adenoma invasion by microbial products, which triggered the production of IL-23 in myeloid cells and promoted the development of a pro-tumoral IL-17 response (Griwniak et al. 2012). In a conditional genetic mouse model of lung adenocarcinoma driven by K-ras activation and p53 inactivation, TAM and TAN precursors were found in the spleen and were physically relocated to the tumor stroma (Cortez-Retamozo et al. 2012). Interestingly, removal of the spleen reduced TAM and TAN accumulation and affected tumor growth, positioning the spleen as a reservoir for TAM and TAN precursors (Cortez-Retamozo et al. 2012). In this model, overproduction of Angiotensin II amplified self-renewing hematopoietic stem cells and macrophage progenitors (Cortez-Retamozo et al. 2013).

In humans, liver epithelial cells from hepatocellular carcinoma (HCC) produce CXC chemokines, notably CXCL8/IL-8, which in turn, promote neutrophil migration in peritumoral stroma (Kuang et al. 2011). Recently, Zhou et al. (2012) conducted an immunohistochemical analysis on 919 HCC patients and found that overexpression of CXCL5 was correlated with neutrophil infiltration, shorter overall survival and tumor recurrence. In addition, head and neck squamous cells carcinoma (HNSSC)-conditioned medium induced neutrophil chemotaxis through IL-8 production and HNSSC-derived macrophage migration inhibitory factor (MIF) induced neutrophil recruitment in a CXCR2-dependent manner (Dumitru et al. 2011; Trelakis et al. 2011).

**Roles of macrophages in cancer**

Plasticity is a well-known characteristic of macrophages and consists on their ability to integrate distinct signals from the microenvironment and to acquire distinct phenotypes (Sica and Mantovani 2012). In a simplistic point of view, macrophages may result in two opposite polarization states. Typical Th1 cytokines (e.g. IFN-γ) alone or combined with microbial components (e.g. LPS) give rise to M1 macrophages, which play a classic role in Th1 response and in mediating resistance against microbes and tumor cells. These M1 polarized macrophages efficiently produce effector molecules (e.g. reactive oxygen and nitrogen intermediates) and inflammatory cytokines (e.g. IL-1β, TNF-α, IL-6) and are characterized by a high production of IL-12 and low expression of IL-10 (Sica and Mantovani 2012). Consistent with these functions, M1 macrophages produce chemokines such as CXCL9/Mig and CXCL10/IP-10, which attract Th1 lymphocytes. On the other hand, IL-4 and IL-13 inhibit this classical activation and induce the alternative M2 form of macrophage polarization (Gordon and Taylor 2005). M2 macrophages are characterized by a high production of IL-10, low expression of IL-12 and a poor antigen presenting capacity (Noel et al. 2004). M2 macrophages produce chemokines such as CCL17/TARC, CCL22/MDC and CCL24/Eotaxin-2, involved in Treg cell, Th2, eosinophil and basophil recruitment (Mantovani et al. 2002; Martinez et al. 2006; Romagnani et al. 1999). Moreover, they suppress Th1 adaptive immunity, participate in the resolution of inflammation, in the protection against parasites, promote wound healing, angiogenesis and tissue remodeling (Biswas and Mantovani 2010). A strong evidence of macrophage plasticity consists in their potential to be "re-programmed" by some immunological stimuli, such as IFN-γ or IFN-α, from immunosuppressive M2 macrophages into immunostimulatory cells (De Palma et al. 2008; Duluc et al. 2005). As mentioned above, macrophages infiltrating the tumor may display dual functions but several lines of evidence indicate that they take part into the inflammatory process, which favors tumor formation and progression and, accordingly, several studies have reported that TAM have a M2-like phenotype (Biswas et al. 2006).

Many functions have been attributed to macrophages during tumor growth and progression, including extracellular matrix remodeling, promotion of tumor cell invasion and metastasis, angiogenesis, lymphangiogenesis and immune suppression (Mantovani et al. 2002) (Fig. 1 and Table 1).

TAM produce a number of proteolytic molecules, such as plasmin, urokinase-type plasminogen activator, cathepsin B and matrix metalloproteases (MMP) which may directly remodel the ECM (Gocheva et al. 2010; Nagakawa et al. 2002; Wang et al. 2011).
For instance, MMP have been implicated in tumor progression due to their capacity to degrade the basement membrane, to activate growth factors and to enhance angiogenesis (Huang et al. 2002; Stettler-Stevenson and Yu 2001; Wang et al. 2005). In addition, TAM may favor the invasiveness of cancer cells through the expression of non-proteolytic molecules. For instance, expression of chemokines that bind CXCR2 was increased in macrophages exposed to conditioned media from mammary epithelial cells containing FGF receptor 1-induced soluble factors. In turn, these chemokines induced migration of primary and tumoral mammary epithelial cells (Bohrer and Schwertfeger 2012). In mice injected subcutaneously with pancreatic cancer cells, expression of scavenger-receptor A in hematopoietic cells, consistent with its expression on macrophages, was required for cancer metastasis (Neyen et al. 2013). Moreover, macrophages-derived TGF-β1 promoted the expression of MMP-9 in glioma stem-like cells and thus, increased the invasiveness of tumor cells (Ye et al. 2012). Finally, tumor-derived versican V1 enhanced the expression of the antimicrobial peptide hCAP18/LL37 in macrophages, which in turn contributed to ovarian tumor cell proliferation and invasion (Li et al. 2013).

As mentioned above, macrophages have been described to be associated with the metastatic potential of several tumors (Lin et al. 2011; Qing et al. 2012). For instance, transfer of thioglycollate-elicted peritoneal macrophages in mice increased by up to 100-fold the number of artificially induced metastatic lung nodules induced by the intravenous injection of melanoma or Lewis lung carcinoma tumor cells (Gorelik et al. 1982). In a mouse model of breast cancer, IL-4-treated macrophages upregulated the expression of cytokine protease cathepsin B, which promoted lung metastasis (Vasiljeva et al. 2006). Moreover, macrophages exposed to M2 polarizing cytokines or tumor cells conditioned media, express a truncated fibronectin isoform, namely migration-stimulating factor (MSF), which exert a potent chemotactic effect on tumor cells (Solinas et al. 2010). The metastatic potential of TAM is further supported by depletion studies demonstrating a reduced incidence of metastasis (DeNardo et al. 2009; Joyce and Pollard 2009).

A number of evidence have shown that TAM are associated with tumor angiogenesis and lymphangiogenesis. Indeed, TAM express mediators such as TGF-β, VEGF-A, VEGF-C, PDGF, MMP-9, thymidine phosphorylase (TP) and chemokines (e.g. CXCL8/IL-8) which are directly or indirectly involved in new vessel formation and sprouting (Granata et al. 2010; Hotchkiss et al. 2003; Lin et al. 2006; Murdoch et al. 2008; Schmidt and Carmeliet 2010; Schoppmenn et al. 2002). For instance, TAM-derived MMP-9 induces the release of heparin-bound growth factors, particularly VEGF-A, crucial for the angiogenic switch (Ebrahem et al. 2010). In the tumor microenvironment, the increasing expression levels of HIF-1 and HIF-2 induced by low-oxygen tension triggers a pro-angiogenic program in macrophages characterized by high expression levels of VEGF, bFGF, CXCL8/IL-8 and glycolytic enzymes (Murdoch et al. 2004). Moreover, angiogenic and lymphangiogenic factors are released by human macrophages in response to high levels of adenosine, which are present in the tumor microenvironment during local hypoxia (Granata et al. 2010). The angiogenic potential of TAM has been further proved by depletion studies demonstrating a reduced blood vessel density in tumor environment (Zeisberger et al. 2006).

TAM exert also an immunosuppressive activity, through the expression of a wide range of molecules, such as TGF-β, iNOS,
arginase-1, IDO and IL-10, known for their immunosuppressive role (Hagemann et al. 2006; Mantovani and Sica 2010; Sica et al. 2000; Zhao et al. 2012a,b). In murine models of breast cancer, T cell suppression is dependent, at least in part, on TAM metabolic activities via arginase-1 or iNOS expression (Bronte and Zanovello 2005; Chang et al. 2001; Doedens et al. 2010; Movahedi et al. 2010). However and particularly in humans, TAM-mediated T cell suppression may also occur irrespectively of the l-arginine metabolism (Kryczek et al. 2006). For instance, TAM have been shown to express the immunosuppressive molecule B7-H1 in hepatocellular carcinoma, B7-H4 in ovarian and lung cancer and B7-H3 in lung cancer (Chen et al. 2012, 2013; Kryczek et al. 2006; Kuang et al. 2009). In addition, TAM have the capacity to induce the expression of these molecules on cancer cell surface, thus providing a novel mechanism by which cancer cells escape the immune surveillance (Chen et al. 2013).

Due to their overall pro-tumoral effects, targeting TAM is a useful and promising tool for new anti-tumoral therapies. Accordingly, several therapeutic strategies were proposed to inhibit their recruitment, interfere with their survival, or reprogram them into a M1 anti-tumoral phenotype (Beaty et al. 2011; Edwards and Emens 2010; Germano et al. 2013; Rozet et al. 2009; Xin et al. 2009).

Role of neutrophils in cancer

In addition to the well-characterized TAM, neutrophils have recently emerged as new tumor-infiltrating myeloid cells, playing an important role in tumor growth and progression (Mantovani et al. 2011) (Fig. 2 and Tables 1 and 2). Similarly to their myeloid “cousins” macrophages, also neutrophils may have both pro-tumoral and anti-tumoral roles.

Genetic instability is a hallmark of cancer and evidence has indicated that neutrophils are involved in the process of carcinogenesis through the release of nitric oxide derivatives and reactive oxygen species (ROS) (Gungor et al. 2010; Hanahan and Weinberg 2011; Sandhu et al. 2000). Accordingly, neutrophil-derived ROS, such as the MPO-mediated formation of HOCl, have been associated with point mutations and DNA damage (Gungor et al. 2010). In addition, HOCl may also activate several proteolytic enzymes, such as MMP-2, MMP-7, MMP-8 and MMP-9 and inactivate the tissue inhibitor of metalloprotease 1 (TIMP-1), thus enhancing the activity of MMP-9 and favoring the invasiveness of cancer cells (De Larco et al. 2004).

Neutrophil-derived cytokines and proteins stored within granules may also play a dual role in tumor progression. For instance, neutrophil elastase (NE) was taken up by adjacent epithelial lung cancer cells and favored tumor cell proliferation through the hydrolysis of the insulin receptor substrate-1 (IRS-1), which usually blocks PI3K activity and reduces PDGFR signaling (Houghton et al. 2010). NE has also been involved in neutrophil-mediated epithelial-to-mesenchymal-transition (Grosse-Steffen et al. 2012). In contrast, in breast cancer cells, NE cleaved cyclin E in a truncated isoform, which is presented in the context of HLA-I and promoted a T lymphocyte-mediated lysis of tumor cells (Mittendorf et al. 2012).

Breast cancer cell-derived GM-CSF induced the production of oncostatin M (OSM) in neutrophils, which in turn stimulated breast cancer cells to release VEGF, promoted cancer cell detachment and enhanced their invasive behavior (Queen et al. 2005). In bronchoalveolar carcinoma, tumor derived cytokines (i.e. TNF-α, GM-CSF) induced the release of hepatocyte growth factor (HGF) by neutrophils, which enhanced tumor cell migration. Accordingly, patient bronchoalveolar lavage fluid levels of HGF were found correlated with neutrophil counts and associated with poor prognosis (Wislez et al. 2003). In addition, neutrophils enhanced the invasive capacity of human cholangiocellular carcinoma cells and hepatocellular carcinoma through the expression of HGF (Imai et al. 2005). In oropharynx sinus carcinoma patients, simultaneous presence of a high number of neutrophils and a high expression level of COR-TACTIN, a protein involved in cellular invasion and migration, has been associated with poor clinical outcome (Dumitru et al. 2013). Acquisition of metastatic behavior of benign murine fibrosarcoma cells has also been related to the neutrophil infiltration (Tazawa et al. 2003). Finally, melanoma cells expressed CXCL8/IL-8, which attracted neutrophils and promoted the expression of β2 integrin on their surface. In turn, β2 integrin interacted with ICAM-1 expressed on melanoma cells, favoring the lung metastasis development. It is likely that this interaction increased the entrapment of melanoma cells within the circulation to facilitate their adhesion to vascular endothelium, their extravasation and thus to promote development of metastasis (Huh et al. 2010). In contrast, in mice orthotopically implanted with breast cancer cells, neutrophils were found accumulated in the premetastatic lung and their depletion increased the metastatic load (Granto et al. 2011). The authors proposed that tumor entrained neutrophils (TEN) recruited in the premetastatic lung prevented tumor cell seeding through an H2O2–dependent mechanism (Granto et al. 2011). Moreover, TEN acquired a cytotoxic phenotype and killed tumor cells following stimulation by G-CSF and tumor-secreted CCL2 (Granto et al. 2011).

Neutrophils express also a wide armamentarium of angiogenic factors able to modulate tumor angiogenesis. For instance, CXCL1/MIP-2 recruits neutrophils that, in turn, release biologically active VEGF-A, resulting in angiogenesis in vivo (Scapini et al. 2004). In addition, in models of subcutaneous melanoma or fibrosarcoma,
TAN expressed high levels of the homing receptor CXCR4 and regulated angiogenesis and tumor growth through high expression levels of the angiogenic factors VEGF and MMP-9 (Jablonska et al. 2010). IFN-β, known to modulate tumor growth, controlled the expression levels of these molecules in vivo (Jablonska et al. 2010).

In a tumor-xenograft model, expression of Bv8 (prokineticin-2), which supports neutrophil mobilization and angiogenesis, is upregulated in a G-CSF dependent manner (Shojaei et al. 2007). Accordingly, blocking Bv8 reduced peripheral blood and tumor-infiltrating neutrophils, suppressed angiogenesis and tumor growth (Shojaei et al. 2007). Interestingly, a high neutrophil infiltration is found in tumors refractory to anti-VEGF therapy in which G-CSF-induced Bv8 promotes resistance (Shojaei et al. 2008, 2009).

TAN release proteases involved in tumor growth. For instance, neutrophil-derived MMP-9 has been involved in the angiogenic switch through the release of VEGF from the ECM and neutrophils were identified as the major source of MMP-9 in human head and neck cancer and hepatocellular carcinoma (Dumitru et al. 2012; Kuang et al. 2011; Nozawa et al. 2006). Interestingly, MMP-9 is released by neutrophils in a TIMP1-free manner, thus providing a powerful pro-angiogenic factor (Ardi et al. 2007). Accordingly, TAN were found correlated with tumor angiogenesis and their depletion reduced tumor growth and angiogenesis (Kuang et al. 2011). In contrast, a potential anti-angiogenic and anti-tumoral role for MMP-9 has been recently proposed in a xenograft model of breast cancer (Leifier et al. 2013). Indeed, adenoviral gene transfer of MMP-9 caused a dose-dependent massive infiltration of neutrophils inside the tumor and, surprisingly, a reduction of tumor growth and angiogenesis. Interestingly, neutrophil depletion abrogated this therapeutic activity of AdMMP-9, whereas gene transfer of TIMP-1 did not exert any effect (Leifier et al. 2013).

Neutrophils are also a source of anti-angiogenic mediators, such as elastase, which promotes the degradation of VEGF-A, bFGF and α-defensins (Ai et al. 2007; Chavakis et al. 2004; Scapini et al. 2002). In addition neutrophil-derived elastase is responsible for the generation of angiostatin-like fragments (i.e. Kringle domain 1 to Kringle domain 3) from plasminogen (Scapini et al. 2002). These peptides have the capacity to inhibit the proliferation of endothelial cells and angiogenesis induced by VEGF and bFGF (Scapini et al. 2002).

TNF-related Apoptosis-Inducing Ligand (TRAIL), which possesses anti-tumoral activity, is expressed by neutrophils, (reviewed in Cassatella 2006; Tecchio et al. 2013). Interestingly, neutrophils released TRAIL after mobilization of the intracellular pool induced by Mycobacterium bovis Bacillus Calmette–Guerin (BCG), demonstrating a potential role of neutrophils in BCG immunotherapy for superficial bladder cancer (Kemp et al. 2005). Moreover, TRAIL was released by IFN-α-stimulated neutrophils isolated from Chronic Myeloid Leukemia (CML) patients and induced apoptosis of TRAIL-sensitive leukemia cells (Tanaka et al. 2007; Tecchio et al. 2004).

Several studies have demonstrated the capacity of mouse neutrophils to produce IL-10 (Tosello Boari et al. 2012; Tsuda et al. 2004; Zhang et al. 2009). Despite previous negative findings (Cassatella et al. 2009), the presence of human immunosuppressive neutrophils, able to produce remarkable amounts of IL-10 in response to increasing concentrations of serum amyloid A, has been described in melanoma patients (De Santo et al. 2010). However, other groups did not confirm these findings and emphasized the need for stringent neutrophils purification devoid of monocyte contamination (Davey et al. 2011). Moreover, recent evidence showed that human neutrophils present an inactive IL-10 genetic locus, supporting their incapacity to produce IL-10 (Tamassia et al. 2013).

Mirroring the morphagocyte plasticity, Fridlender et al. (2009) have demonstrated that TGF-β drives neutrophils to acquire a protumoral “N2” phenotype, whereas TGF-β inhibition enhances the emergence of an anti-tumoral “N1” phenotype, characterized by cytotoxic activity on cancer cells and an immunostimulatory profile (i.e. TNF-α/high, CCL3/high, ICAM-1/high, arginase(low)). More recently, GM-CSF has been proposed to differentiate murine neutrophils in “hybrid” population displaying phenotype and functional properties of neutrophils and dendritic cells (DC) together (Geng et al. 2013; Matsushima et al. 2013).

It is important to keep in mind that existence and functional aspects of neutrophil polarization in humans need to be carefully investigated. Interestingly and as observed in mice, human neutrophils acquired a DC-like phenotype in the presence of GM-CSF, TNF-α and IL-4 (Oehler et al. 1998). Collectively this increasing body of evidence emphasizes the high versatility of neutrophils depending on the context and could offer new therapeutic approaches. Accordingly, blocking neutrophil recruitment or neutralizing their effector molecules has been proposed as anti-tumoral therapeutic

![Diagram](image-url)
strategies (Citro et al. 2012; Gregory and Houghton 2011; Jamieson et al. 2012). However, therapeutic depletion of neutrophils could lead to immunosuppressive state and new therapeutic approaches should enhance their cytotoxic activity (van Egmond and Bakema 2012).

A schematic view of neutrophil-derived mediators and their role in tumor progression or regression is provided in Fig. 1 and Table 2.

Prognostic significance of TAM and TAN in cancer

Prognostic significance of TAM in humans has been recently critically evaluated (Zhang et al. 2012). Epidemiological evidence revealed that high numbers of TAM are significantly associated with poor patient prognosis in a wide spectrum of human cancers, such as breast, cervix, bladder and gastric (Bingle et al. 2002; Qian and Pollard 2010). In contrast, other studies have reported that the prognostic significance of TAM can be controversial (Zhang et al. 2012). For instance, statistically significant correlation between CD68+ cells and better survival was found in high-grade osteosarcoma patients, whereas any statistically significant correlation was found between the number of CD68+ cells and clinical outcome in patients with large B-cell lymphoma (Buddingh et al. 2011; Hasselblom et al. 2008). In gastric cancer, number of TAM has been positively correlated with tumor cell apoptosis and the presence of CD8-positive cells (Ohno et al. 2003). Moreover, the number of TAM was found to be an independent predictor of patient better survival (Ohno et al. 2003). The prognostic significance of TAM in patient with colorectal cancer (CRC) is controversial and could depend on distinct phenotypes acquired on distinct localization within the tumor (Erreni et al. 2011). It is also important to keep in mind that heterogeneity between studies (i.e. experimental procedures and techniques used to identify tissue macrophages) could lead to these controversies (Zhang et al. 2012).

The relationship between TAM infiltration and prognosis in human cancer has been systematically recently discussed (Donskov 2013). Epidemiological evidence has suggested that neutrophil infiltration within human cancers may be associated with a poor clinical outcome, as observed in patients with metastatic and localized clear cell carcinomas, bronchioloalveolar carcinoma, hepatocellular carcinoma, colorectal carcinoma and head and neck squamous cell carcinoma (Jensen et al. 2009; Kuang et al. 2011; Rao et al. 2012; Trellakis et al. 2011; Wislez et al. 2003). In addition, infiltration of neutrophils has been correlated with the tumor grade in human gliomas and with more aggressive types of pancreatic tumors (Fossati et al. 1999; Reid et al. 2011). Conversely, TAM have been associated with better prognosis in other types of cancers, such as gastric carcinoma (Caruso et al. 2002). As observed for TAM, these results indicate that the prognostic significance of TAM may be different, depending on the type of cancer and on the method used to assess neutrophil density within the tumors (e.g. hematoxylin–eosin stain versus immunohistochemistry) (Caruso et al. 2002; Zhao et al. 2012a,b).

Concluding remarks

A growing number of evidence indicates that tumor growth is closely associated with myeloid cells recruitment, including macrophages and neutrophils. Under the influence of multiple microenvironmental signals, macrophages as well as neutrophils polarize toward distinct phenotypes with pro-tumoral or anti-tumoral activities. Moreover, elucidating the relationship between MDSC, TAM and TAN needs further investigations (Brandau et al. 2013; Fridlender et al. 2012). Expanding our knowledge about the mechanisms used by myeloid cells to modulate tumor growth and progression may be clinically relevant for new therapeutic approaches in cancer.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgments

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