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REVIEW

Cellular and molecular pathways linking inflammation and cancer

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Abstract

Several experimental and epidemiological evidence indicate that, irrespective of the trigger for the development (chronic infection/inflammation or genetic alteration), a "smouldering" inflammation is associated with the most of, if not all, tumours and supports their progression.

Several evidence have highlighted that tumours promote a constant influx of myelomonocytic cells that express inflammatory mediators supporting pro-tumoral functions. Myelomonocytic cells are key orchestrators of cancer-related inflammation associated with proliferation and survival of malignant cells, subversion of adaptive immune response, angiogenesis, stroma remodelling and metastasis formation.

Although the connection between inflammation and cancer is unequivocal the mechanistic basis of such association are largely unknown. Recent advances in the understanding of the cellular and molecular pathways involved in cancer-related inflammation as well as their potential relevance as diagnostic, prognostic and therapeutic targets are herein discussed.

Keywords: Cancer; Cytokines; Inflammation; MDSCs; NF-κB; TAMs; STATs

Contents

Abbreviations: COX-2, cycloxygenase-2; TGFβ, transforming growth factor-β; HIF-1, hypoxia inducible factor 1; STAT-3, signal transducers and activator of transcription-3; TAMs, tumour-associated macrophages; TNFalpha, tumour necrosis factor alpha; TEMs, Tie2-expressing monocytes; MDSC, myeloid-derived suppressor cells; NO, nitric oxide; ROI, reactive oxygen intermediates; TLR, toll-like receptor; VEGF, vascular endothelial growth factor; MMPs, metalloproteinase; Ang-2, angiopoietin-2; GM-CSF, granulocyte-macrophage colony-stimulating factor; CSF-1, colony-stimulating factor-1; DMBA, 7,12-dimethyl-benz[a]anthracene; NSAIDs, nonsteroidal anti-inflammatory drugs; PGE2, prostaglandin E2..

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Introduction

Although the progress achieved by new diagnostic and therapeutic treatments has led to a declined mortality rate, cancers remain one of the major cause of death in industrialized countries. The progressive sequence of mutations and epigenetic alterations of cancer-related genes promote the malignant transformation of cancer progenitor cells by disrupting key processes that are involved in the control of normal cell growth and tissue homeostasis. In addiction to genetic alterations, inflammatory cells and circuits characterize the tumour microenvironment and represent crucial players in the tumour development and progression (Balkwill et al. 2005; Balkwill and Mantovani 2001; Coussens and Werb 2002; Karin 2006).

The inflammation–cancer link can be view as consisting of two pathways: an extrinsic pathway driven by inflammatory signals (e.g. infections) and autoimmune diseases (e.g. inflammatory bowel disease) and an intrinsic pathway driven by genetic alterations that cause both inflammation and neoplasia (Mantovani et al. 2008). Thus, irrespective of the trigger for the development, the presence of inflammatory cells and mediators in tumour tissues, tissue remodelling and angiogenesis similar to that seen in chronic inflammatory responses and tissue repair are hallmarks of most of, if not all tumours. Several studies have highlighted that a leukocytes infiltrate, varying in size, composition and distribution is present in the majority of tumours and is involved in carcinogenesis, tumour growth, invasion and metastasis (Coussens et al. 2000; Lin et al. 2001; Mantovani et al. 1992). In particular tumour growth is paralleled by recruitment and accumulation of myelomonocytic cells; macrophages in particular (Sica and Bronte 2007).

Altough these cells have the ability to prevent the establishment and the spread of tumour cells, several evidence indicate that, in established cancers, these cells acquire functions supporting tumour growth and dissemination (Mantovani et al. 2004 2002; Sica et al. 2006). Their phenotypic switch during tumour development may depend on the functional plasticity characterizing these cells. Indeed, in response to different microenvironmental signals macrophages can express different "polarized" functional programs (Mantovani et al. 2005). However, up to date, the tumour-derived signals promoting the skewing of myeloid cell functions are poorly known.

In this review we discuss current knowledge about the cellular and molecular basis promoting cancer-related inflammation. The elucidation of these mechanisms may offer the opportunity to develop strategies and drugs that could act in synergism with conventional therapeutics and further overcome the problems due to the high grade of genetic instability of characterized malignant cells.

Inflammation and cancer connection

Chronic inflammation represents a major pathological basis for tumour development. Although inflammation acts as host defence mechanism against infection or injury and is primarily a self limiting process, inadequate resolution of inflammatory responses lead to various chronic disorders associated with cancers. In 1863, Rudolf Virchow proposed that chronic inflammation supports cancerogenesis. Since then, accumulating studies support this hypothesis and it is estimated that 20% of all cancers death are associated with chronic infection and inflammation. Microbial infections (e.g. *Helicobacter pylori* is associated with gastric cancer and gastric mucosal lymphoma), viral infections (e.g. hepatitis B or C virus are associated with hepatocellular carcinoma), autoimmune disease (e.g. inflammatory bowel disease is associated with colon cancer) and inflammatory conditions of unknown origin (e.g. prostatitis is associated with prostate cancer) are recognized as triggers of chronic inflammation associated with cancer development (Mantovani et al. 2008). In line with the pro-tumoral role of chronic inflamma-

tion, epidemiological studies have highlighted that the treatment with nonsteroidal anti-inflammatory agents, such as cycloxygenase-2 (COX-2) inhibitors, reduce the risk of developing certain cancers (such as colon and breast cancer) and the mortality caused by these cancers (Chan et al. 2004, 2007; Flossmann and Rothwell 2007; Koehne and Dubois 2004). In addition a "smouldering" inflammation is present in tumours not causally related to an obvious inflammatory process (intrinsic pathway). Recent evidence has indeed demonstrated that the expression of the inflammation-related programs is driven by the activation of different classes of oncogenes. For example, the chromosome rearrangement leading to the ligand independent activation of the tyrosine kinase RET is a frequent early event in the pathogenesis of the papillary thyroid carcinoma. Borrello and colleagues observed that in freshly isolated human thyrocytes, activation of the oncogene RET promotes the same inflammatory transcriptional program found in patients affected by papillary thyroid carcinoma (Borrello et al. 2005). In analogy, other oncogenes, (e.g. RAS and MYC) and tumour-suppressor genes, (e.g. von Hippel-Lindau tumour suppressor (VHL), transforming growth factor-β (TGFβ) and phosphatase and tensin homologue (PTEN)), activate signalling pathways involved in inflammation (Ancrile et al. 2007; Balkwill 2004; Guerra et al. 2007; Kobielak and Fuchs 2006; Phillips et al. 2005; Schioppa et al. 2003; Shchors et al. 2006; Soucek et al. 2007).

Both extrinsic and intrinsic pathways of cancer-related inflammation activate transcription factors (mainly NF-κB, HIF-1α, STAT3), which are the key inducers of inflammatory mediators (e.g. cytokines, chemokines, prostaglandins and nitric oxide) (Mantovani et al. 2008). The switch to "smouldering" inflammation contributes to tumour development through different mechanisms, including induction of genomic instability, alteration in epigenetic events and subsequent inappropriate gene expression, enhanced proliferation and resistance to apoptosis of initiated cells, induction of tumour angiogenesis and tissue remodelling with consequent promotion of tumour cells invasion and metastasis (Mantovani et al. 2008) (Fig. 1).

Despite this evidence, genetic studies of mouse models have demonstrated that the inflammatory response supported by innate immune cells is crucial for the activation of an adaptive immune response capable to eliminate nascent tumours (Dunn et al. 2002). It is generally accepted that immune cells continuously recognize and destroy nascent tumour cells but, due to the genetic instability that characterize neoplastic cells, the arising of new variants able to evade the immune surveillance results in tumour establishment and progression ("immunoediting" process) (Dunn et al. 2002). In this regard several studies aim to elucidate the mechanisms driving immune escape. They emphasise

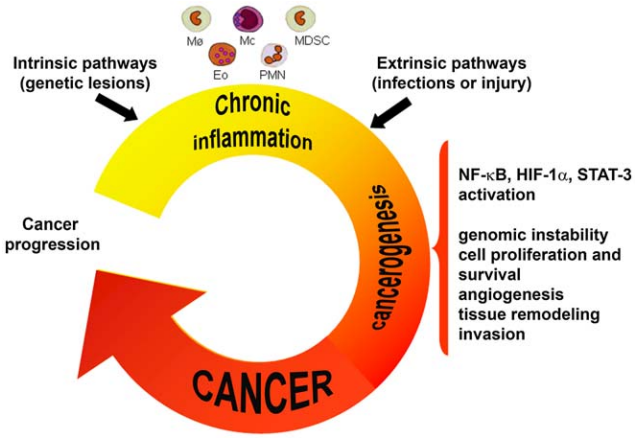

Fig. 1. Inflammation and cancer connection. Irrespective of the trigger for the development both intrinsic (driven by genetic alteration) and extrinsic (driven by inflammatory cells and mediators) pathways result in inflammation and neoplasia. Both neoplastic cells and leukocytes, mainly belonging to the myelomonocytes lineage, contribute to the "smouldering" inflammation associated with tumour initiation and progression. The transcription factors NF-κB, HIF-1α and STAT-3 are key modulators of the inflammatory response that promotes cancer development through different mechanisms including induction of genomic instability, alteration in epigenetic events and subsequent inappropriate gene expression, enhanced proliferation and resistance to apoptosis of initiated cells, induction of tumour angiogenesis and tissue remodelling with consequent promotion of tumour cells invasion and metastasis. (Mø, macrophages; Mc, mast cells; MDSC, myeloid derived suppressor cells; Eo, eosinophil; PMN, polymorphonuclear cells).

that the smouldering inflammation associated with established tumours tunes the adaptive immune response. Indeed, tumour-associated dendritic cells mainly show an immature phenotype (Allavena et al. 2000) and myelomonocytic cells recruited in tumours express an alternative M2 functional phenotype, mainly oriented towards the suppression of the adaptive immune response (Mantovani et al. 2009; Sica et al. 2006).

Tumour-associated myelomonocytic cells

Tumour-derived factors, which cause sustained myelopoiesis, accumulation and functional differentiation of myelomonocytic cells, provide an essential support for the angiogenesis and the stroma remodelling required for tumour growth (Mantovani et al. 2009; Sica and Bronte 2007). Whereas tumour-associated macrophages (TAM) represent the major population of inflammatory cells infiltrating tumours, several studies indicate that Tie2-expressing monocytes (TEM) and myeloid-derived suppressor cells (MDSC) are also involved in the promotion of tumour growth, dissemination and metastasis (Fig. 2).

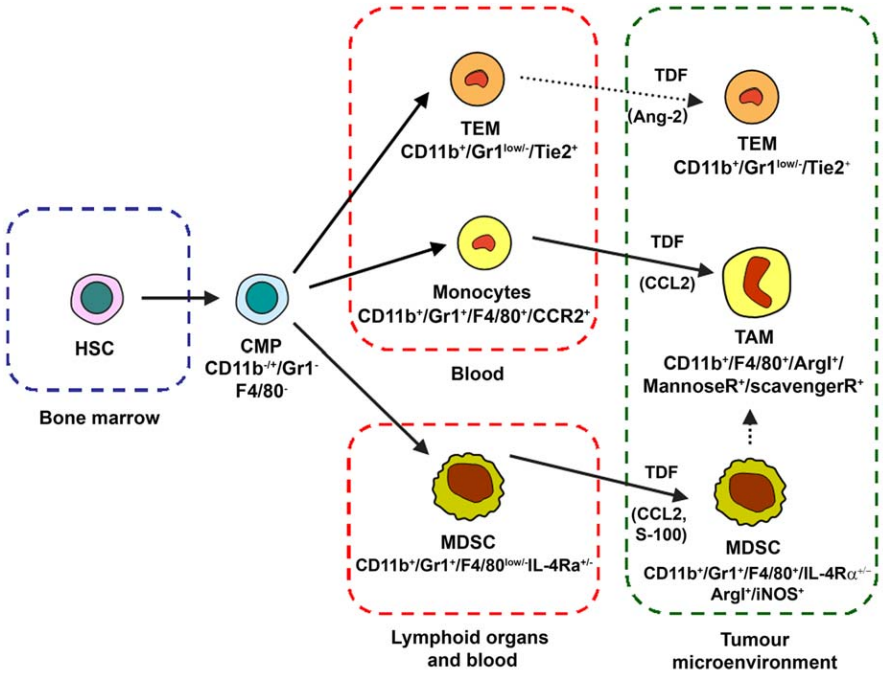

Fig. 2. Tumour-derived factors (TDFs) sustain the myelopoiesis as well as the accumulation and functional differentiation of myelomonocytic cells. HSCs give rise to common myeloid precursors (CMPs), which subsequently originate at least three different subsets of cells circulating in tumour-bearing hosts: monocytes ($CD11b^+/Gr1^+/F4/80^+/CCR2^+$), TEM ($CD11b^+/Gr1^{low/-}/Tie2^+$) and MDSCs ($CD11b^+/Gr1^+/F4/80^{low/-}/IL\text{-}4R\alpha^{+/-}$). Circulating monocytes are recruited by TDFs (mainly CCL2) and differentiated into TAMs, acquiring pro-tumoural functions. TEMs, mainly clustered in highly vascularised tumours area, are key orchestrators of tumour angiogenesis; they likely derived by circulating TEMs recruited in tumours by chemotactic factors such as Ang2. MDSC, accumulating in blood and lymphoid organs during tumour progression, may also be recruited to the tumour microenvironment (CCL2, S-100), where they contribute to suppression of the adaptive immune response.

Tumour-associated macrophages

The tumour-promoting role of TAM was suggested by the association between high frequency of infiltrating TAM and the poor prognosis for many different human tumours such as lymphoma, cervix, bladder, breast and lung cancers (Bingle et al. 2002). Accordingly with these findings, in the post-genomic era, genes associated to leukocytes or macrophages infiltration (e.g. CD68) were identified as a part of the molecule signatures, which herald to a poor prognosis in lymphomas and breast carcinoma (Paik et al. 2004). In addition, genetically modified mice and cell transfer experiments have provided direct evidence for the pro-tumour functions of TAMs. For example, when MMTV-PyMT mice, which spontaneous develop mammary tumours, were crossed with op/op mice, which lack monocytes/macrophages, the tumour growth and spread were significantly reduced (Lin et al. 2001). In line with their tumour-promoting properties, different drugs able to deplete (Yondelis, clodronate) macrophages or to inhibit their recruitment in tumours (anti-CCL2 antibodies) were considered as anti-tumour strategy. For example, in a preclinical prostate cancer model, the combination of anti-CCL2 antibodies enhanced the therapeutics effects of docetaxel leading to tumour regression (Rozel et al. 2009).

Despite this evidence, macrophages can also express functional programs able to exert cytotoxic activity on tumours. This paradoxical behaviour may be explained by the functional plasticity monocytes/macrophages, which result in the expression of different functional programs in response to different microenvironmental signals (Gordon and Taylor 2005; Mantovani et al. 2002). In analogy with the Th1 and Th2 dichotomy the macrophage-polarized state of activation can be broadly classified as M1 or M2. Classical or M1 macrophage activation in response to microbial products or interferon-γ is characterized by: high capacity to present antigen; high interleukin-12 (IL-12) and -23 (IL-23) production and consequent activation of a polarized type I T cell response (Gordon and Taylor 2005; Mantovani et al. 2002). M1 macrophages have cytotoxic activity towards tumour cells and ingested intracellular microorganisms, by expressing high levels of toxic intermediates, including nitric oxyde (NO), reactive oxygen intermediates (ROI) and tumour necrosis factor alpha (TNFalpha) (Gordon and Taylor 2005; Manto-

vani et al. 2002). In contrast, alternative or M2 activation of macrophages is promoted by various signals (e.g. IL-4, IL-13, glucocorticoids, IL-10, immunoglobulin complexes/TLR ligands), which elicit different M2 forms, sharing a phenotype characterized by an IL-12^{low} IL-10^{high} IL-1 decoyR^{high}, IL-1ra^{high} expression along with high expression of scavenger and mannose receptors (Gordon and Taylor 2005; Mantovani et al. 2002). Furthermore M2 macrophages express a distinct chemokines expression pattern (e.g. CCL17, CCL22) and characteristic change in some metabolic pathways (e.g. arginine methabolism is oriented towards the production of ornitine and polyamine instead of citrulline and NO). Overall the various forms of M2 activated macrophages are oriented to tune M1 inflammation, promoting adaptive Th2 immunity, scavenge debris, angiogenesis, tissue remodelling and repair. Thus, M2-polarized macrophages promote killing and encapsulation of parasites, support wound-healing and express tumour-promoting functions. Which signals drive TAM-polarized activation are not fully elucidated, but several evidence indicate that the cross-talk between tumour cells and macrophages is an essential event. New evidences indicate that macrophage activation switchs during the course of tumour progression (Fig. 3). Whereas the functions of classically activated, 'M1' macrophages, during chronic inflammation appear to predispose a given tissue to tumour initiation (Greten et al. 2004; Pikarsky et al. 2004), in established tumours, macrophages exhibit mainly the alternatively activated 'M2' phenotype and are engaged in immunosuppression and promotion of tumour angiogenesis and metastasis (Mantovani et al. 2004; Sica et al. 2006).

Accordingly with an M2 skewed phenotype, in established tumours, TAM express low levels of inflammatory cytokines (e.g. IL-12, IL-1β, TNFα, IL-6) (Biswas et al. 2006; Mantovani et al. 2004) as well as NO (Dinapoli et al. 1996; Klimp et al. 2001) and ROIs, along with high levels of immunosuppressive cytokines (e.g. IL-10, TGFβ) and scavenger receptors (e.g. SR-A and mannose receptor) (Biswas et al. 2006; Scarpino et al. 2000). This M2 signature along with poor antigen-presenting capacity account for TAM immunosuppressive activities.

The importance of selective polarized inflammatory functions for tumour progression is also supported by evidence suggesting that the type of immunological profile expressed at the tumour site represents an independent prognostic factor. In particular, an established M2 or type-2 "suppressive" immunological profile correlates with poor prognosis, as shown in both colorectal and hepatocellular carcinomas (Budhu et al. 2006; Galon et al. 2006). In this scenario, understanding of tumour-mediated mechanisms promoting polariza-

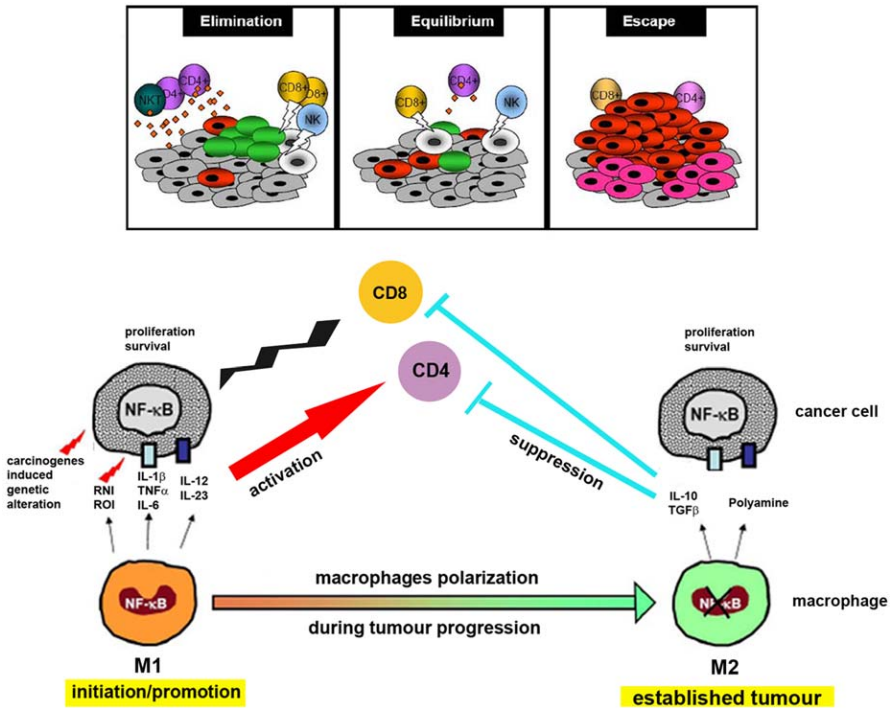

Fig. 3. Macrophages activation switch during the course of tumour progression. Whereas M1 macrophages promote tumour initiation and activate an adaptive immune response capable to eliminate nascent neoplastic cells (elimination phase), tumour progression (equilibrium phase) is paralleled by a gradual switching of macrophage polarization towards the M2 phenotype, which concur to the establishment of permissive conditions for tumour growth and spread (escape phase). The gradual inhibition of NF-κB activity is associated with the M1 versus M2 switching of macrophages polarization.

tion of immune functions is likely to reveal new elements suitable for anticancer strategies.

Approaches based on Toll-like receptor (TLR) agonists, inducers of classical or M1 activation of macrophages, were evaluated for their anti-tumour potential. For example, the combination of the TLR9 agonist CpG plus an anti-IL-10 receptor antibody switched infiltrating macrophages from M2 to M1 functions and triggered innate immune response debulking large tumours within 16 h (Guiducci et al. 2005). In line with this study, several other studies in preclinical models of cancers have confirmed the anti-tumour properties of TLR9 agonists, which are currently used to treat solid and haematologic malignancies (Krieg 2008).

Tie2-expressing monocytes

The generation of new blood vessels in response to the increasing demand for nutrients and oxygen experienced by proliferating tumour cells is essential for tumour growth and progression (Carmeliet and Jain 2000). Myelomonocytic cells, TAM in particular, play a key role in promoting tumour angiogenesis by secretion of several growth and matrix remodelling factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), urokinase type plasminogen activator (uPA), metalloproteinase (MMPs), which directly activate endothelial cells proliferation and facilitate their migration within the extracellular matrix (Coussens and Werb 2002; Pollard 2004). Recently, new evidence has highlighted that a distinct subset of monocytes (TEM) characterized by the expression of the Tie-2 receptor, play a key role in the promotion of tumour angiogenesis (De Palma et al. 2005; De Palma et al. 2003; Venneri et al. 2007). In particular De Palma et al. (2005) have generated a transgenic mice that express the conditionally toxic gene herpes symplex virus thymidine kinase (tk) under the control of Tie2 promoter/enhancer. Chimeric mice obtained by transplanting Tie2-tk bone marrow in wild-type recipient mice were inoculated with either mammary tumours or orthotopic human gliomas. Next Ganciclovir was administrated during the early stages of tumour growth to selectively eliminate TEMs. This study showed a significant reduction of both tumour mass and vasculature, demonstrating the importance of TEMs in tumour angiogenesis and growth (De Palma et al. 2005). In both mouse and human, TEMs can be detected at low frequency in peripheral blood (where they represent about the 20% of circulating monocytes) (Murdoch et al. 2007; Venneri et al. 2007). TEMs are clustered in hypoxic areas of solid tumours, in close proximity to nascent tumour vessel. TEMs migrate in response to Angiopoietin-2 (Ang-2) that is upregulated in hypoxic vascular cells of tumours (Murdoch et al. 2007; Venneri et al. 2007). Furthermore Ang-2 along with tumour microenviromental signals such as hypoxia, promotes the angiogenic activity of TEMs. Recent studies have demonstrated that both hypoxia and Ang-2 inhibit TEMs expression of IL-12 and TNFalpha gene products (Murdoch et al. 2007). The tumour-homing ability of TEMs may potentially be used as a vehicle for anti-tumour gene delivery. Recently, this approach was used to deliver IFNalpha to orthotopic human gliomas and spontaneous mouse mammary carcinoma. This approach resulted in significant anti-tumour response and near complet abrogation of metastasis (De Palma et al. 2008).

Myeloid-derived suppressor cells

MDSC were first described in the late 1970s as cells of non-lymphocytic lineage able to suppress T cells functions (Badger et al. 1990; Holda et al. 1985; Strober 1984) and only more recently there has been a resurgence of interest in these cells because of their role in tumour progression and their potential to limit therapeutic responses (Marx 2008).

MDSC have been described both in humans and mice. In human, they were first identified in cancer patients (Apolloni et al. 2000; Kusmartsev and Gabrilovich 2005; Zea et al. 2005) as cells with an immature phenotype expressing CD13, CD33, CD34 and CD11b and being negative for CD14 and HLA-DR. In mice, these cells are usually identified as CD11b and Gr-1 (LY6c and LY6 g) double-positive cells and they can also express CD115, M-CSFR, CD31, CD124 and IL-4Rα (Gallina et al. 2006). It has been shown that LY6c+ and LY6g+ populations might have different functions in cancer (Dietlin et al. 2007; Movahedi et al. 2008; Sawanobori et al. 2008; Zhu et al. 2007).

MDSC derive from common progenitors in the bone marrow and are mobilized in many pathological conditions such as inflammatory diseases, trauma, graft-versus-host disease and tumours, where they accumulate preferentially in blood and spleen with some being recruited directly to the tumour site.

MDSC recruitment and expansion are regulated by several cytokines, chemokines and transcription factors and mechanisms leading to MDSC activation are very complex (Sica and Bronte 2007). It has been demonstrated that among the different chemokines, CCR2 plays a pivotal role in the recruitment and turnover of MDSC in the tumour site (Sawanobori et al. 2008).

In this review, we focused on cancer-related inflammation, which is linked to tumour progression; it is very important to notice that some factors that are found in

the tumour microenvironment such as pro-inflammatory S-100 proteins are crucial for MDSC recruitment. Sinha et al. (2008) demonstrated that MDSC can produce S-100 proteins by themselves, thus providing evidence for an autocrine loop that promotes MDSC recruitment at the site of inflammation (tumour site) in S-100 dependent manner (Cheng et al. 2008).

Bronte et al. (1999) have shown that tumour-derived granulocyte-macrophage colony-stimulating factor (GM-CSF) or the administration of recombinant GM-CSF is sufficient to recruit MDSC in lymphoid organs and suppresses antigen specific CD8 proliferation.

Other factors such as colony-stimulating factor-1 (CSF-1), IL-6, IL-10 and VEGF can regulate MDSC behaviour. CSF-1 recruits suppressive macrophages to the tumour site and macrophages exposed to CSF-1 can induce T cell inhibition through the deprivation of factors such as tryptophan, which are important for T cell proliferation (Wing et al. 1986; Mellor et al. 2003; Mellor and Munn 2003; Mellor and Munn 2004).

Also high levels of IL-6 are associated with poor prognosis in some cancers. IL-6 induces STAT-3, which is a negative regulator of immune functions during tumour development (Trikha et al. 2003; Greten et al. 2004; Stewart and Trinchieri 2009).

VEGF has been directly associated with MDSC recruitment (Melani et al. 2003), and appears an important mediators of the cross-talk between tumour cells and microenvironment, including MDSC (Gabrilovich 2004).

Finally, IL-10 plays a fundamental role in regulating MDSC functions; IL-10 together with TGF-β are considered the key factors released by the tumour (Chen et al. 2001).

It has been shown that IL-10 provides an important signal to induce the suppressive phenotype of MDSC (Gallina et al. 2006). Moreover IL-10 can also be released by MDSC, which can promote the expansion of CD4+FoxP3+ T regulatory cells and provide a signal for macrophages M2 polarization (Huang et al. 2006; Sinha et al. 2007).

The L-arginine pathway is fundamental for MDSC functions. There is a complex and strong relationship between L-arginine (L-Arg) metabolism, immunity and tumourigenesis (Rodriguez and Ochoa 2006), which has been extensively reviewed in other works (Bronte and Zanovello 2005).

Briefly, the two most important enzymes that regulate L-Arg metabolism are arginase (ARG) and nitric oxide (NOS). Arginase is present in two different forms; one inducible and cytoplasmatic (ARG1 or liver arginase) and the other constitutive and mitochondrial (ARG2 or kidney arginase). ARG1 and 2 convert L-Arg in L-ornithine and urea, which are essential for the generation of polyamines, mediated tumour progression (Cederbaum et al. 2004). The presence of MDSC ARG1+ is related to impaired anti-tumour CTL functions (Liu et al. 2003).

The inducible form of NOS (iNOS/NOS2) metabolizes L-Arg in NO and L-citrulline leading to the subsequent production of superoxide as well and can be induced in MDSC by different stimuli such as VEGF, GM-CSF and IL-6 (Bingle et al. 2002; Cruz et al. 2001; Ferret-Bernard et al. 2004; Dawn et al. 2004). The role of NOS2 is dual: on one hand it confers protection towards infections and is expressed by macrophages with M1 phenotype, on the other hand it inhibits T cell activation through the IL-2 receptor pathway (Duhe et al. 1998; Fischer et al. 2001; Bronte et al. 2003). Moreover, MDSC expressing iNOS can inhibit mitogenic and peptide-specific responses through NO production.

Although NOS2 and ARG1 respond to antithetical stimuli and they are mutually exclusive, they can be expressed contemporarily in MDSC (Gallina et al. 2006) leading to at least one mechanism of suppression that involves both of them (Bronte et al. 2003). In fact, ARG1 increases the levels of superoxide production in MDSC through a pathway that involves iNOS and this superoxide is required for ARG1 mediated suppression of T cell functions and leads to both T cell and IL-2 receptor disfunction (Bronte et al. 2003).

Finally, MDSC can mediate immune suppression also through ROS. ROS, as iNOS, can be induced by tumour-derived factors such as TGF-β , IL-6, GM-CSF and IL-10. It has been shown that inhibition of ROS can abrogate the suppressive functions of MDSC *in vitro* (Kusmartsev et al. 2004).

Since MDSC exert very potent immune suppression, various groups have recently attempted to overcome these mechanisms through different strategies, including *in vivo* depletion of MDSC, pharmacological inhibition of suppressive functions and induction of fully mature dendritic cells.

It has been shown that accumulation of MDSC is sufficient to confer refractoriness to anti-VEGF treatment in some tumours. Shojaei et al. (2007) show that the combination of anti-VEGF antibody with a monoclonal antibody that targets myeloid cells is able to inhibit the growth of refractory tumours more effectively than anti-VEGF alone.

Moreover, antibodies against S100-A8 and S-100-A9 proteins are able to inhibit MDSC recruitment to the tumour site (Sinha et al. 2008; Cheng et al. 2008). Finally, Suzuki et al. (2005) used the chemotherapy drug Gemcitabine to eliminate Gr-1 CD11b cells from the spleen of tumour-bearing animals showing that the loss of MDSC was accompanied by an increase in anti-tumour activity of CD8T cells and NK cells.

Nevertheless, despite advances in phenotypic characterization of MDSC, much remains to be investigated, for example, the molecular basis underlying the pro-tumoural phenotype of these cells.

Molecular links between inflammation and cancer

Studies of genetically modified mice, experiment of inflammatory cells adoptive transfer and analysis of human tumours have highlighted some of the molecular pathways that link inflammation and cancers. Cytokines, chemokines, lipid mediators, nitric oxide (NO) intermediates and the transcription factors NF-κB, hypoxia inducible factor 1α (HIF-1α) and signal transducers and activator of transcription-3 (STAT-3) represent the major molecular players linking inflammation and cancers (Kundu and Surh 2008; Mantovani et al. 2008). Experimental evidence supporting the importance of these molecules in cancer-related inflammation along with preclinical and early phase I/II clinical trials with drugs are hereafter discussed.

Cytokines

TNFalpha plays a dual role in carcinogenesis. Whereas high concentration of this cytokine is able to kill endothelial as well as tumour cells, in certain tumour models, it stimulates fibroblasts or tumour cell growth (Gaiotti et al. 2000). Direct evidence of the pro-tumoural role of TNFalpha came from the observation that mice lacking this cytokine (Moore et al. 1999) or its receptor (Arnott et al. 2004) are resistant to skin carcinogenesis. Higher expression of TNFalpha was further observed in gastric lesion (Noach et al. 1994) and inflamed colonic mucosa (Noguchi et al. 1998) obtained from patients with *H. pylori* infection and inflammatory bowel diseases, which are predisposing conditions for the development of gastric and colorectal tumours respectively. Furthermost recent evidence suggest that TNFalpha is also involved in tumour spread. *In vitro* co-culture experiments have indeed demonstrated that macrophages promote invasiveness of tumour cells by a TNFalpha dependent matrix metalloproteinase induction (Pollard 2004).

Similarly to TNFalpha, IL-1beta role in cancer associated inflammation is controversial. Whereas a low concentration of IL-1beta may induce a local inflammatory response leading to activation of protective immune response, high concentration of IL-1beta results in inflammation-associated cancer damage (Apte and Voronov 2002). The importance of IL-1beta in tumour spread was demonstrated by the observation that metastasis associated with melanoma, mammary and prostate cancer models were inhibited in IL-1beta deficient mice (Giavazzi et al. 1990).

Several lines of evidence indicate that IL-6 is part of the inflammatory pathways promoting cancer initiation and progression. The observation of increased IL-6 levels in the serum of cancer patients (Chung and Chang 2003) or in tumour biopsy (Kai et al. 2005) has indeed suggested a role of this cytokine in cancer-related inflammation. Recent, studies with genetically modified mice highlights the importance of IL-6 in different models of carcinogenesis (Ancrile et al. 2007). Using both a human kidney cell implanted model and a DMBA-TPA-induced skin carcinogenesis model Ancrile et al. (2007) demonstrated that IL-6 induction by ras is crucial for tumour growth. The importance of IL-6 in a colitis-associated cancer (CAC) model has been demonstrated by other recent studies (Bollrath et al. 2009; Grivennikov et al. 2009). Using genetic tools, they demonstrated that IL-6, mainly produced by lamina propria myeloid cells, promotes proliferation and survival of premalignant intestinal epithelial cells, thus enhancing both initiation and progression of CAC (Bollrath et al. 2009; Grivennikov et al. 2009).

The role of IL-7 and IL-17 in cancer-related inflammation are directly associated with the role played by Th17T cells in tumour development. Whereas IL-17 promotes survival (Tartour et al. 1999), fibrosarcoma (Numasaki et al. 2003) and small lung cell carcinoma (Numasaki et al. 2005) development through the enhancement of angiogenesis, IL-17 can also inhibit tumour cell growth due to the recruitment of T cells with cytotoxic activity against tumour (Benchetrit et al. 2002). In line with the anti-tumour role of Il-17 activities, studies by Muranski et al. (2008) demonstrated that adoptive transfer of Th17 cells was the most potent in mediating tumour regression as compared with Th0 or Th1 cells.

Chemokines

Chemokine receptors and their ligands are key orchestrators of leukocytes trafficking in homeostatic conditions as well as during inflammation and cancer. Further evidence has highlighted that chemokine and their receptors are part of the molecular pathways that drive cancer cell motility, invasiveness and survival. Cancer cells produce chemokines such as CCL2, which is the pivotal factor for monocytes recruitment, which in turn supports tumour growth and spread. Further, as results of their malignant transformation and/or in response to tumour hypoxia (e.g CXCR4 induction) (Schioppa et al. 2003), they also acquired the expression of chemokine receptors important for their migration to and survival at sites that are distant from the primary tumour. For example, the chemokines receptor CXCR4 is frequently upregulated by malignant cells and for different types of tumours (colorectal, breast, liver and oesophageal cancers) its expression levels by primary tumours correlate with the frequency of lymphonodes metastasis (Kaifi et al. 2005; Kim et al. 2005; Salvucci et al. 2006). Similarly, a strong correlation between

chemokine receptor expression and organ-specific metastasis has been described for many different types of solid cancers (Burns et al. 2006; Kawada et al. 2004; Marchesi et al. 2008; Shields et al. 2007; Shulby et al. 2004; Zipin-Roitman et al. 2007). This evidence indicates that the chemokine axis is specific both for the cancer cell type and the target organ. For example, in breast cancer, expression of both CXCR4 and CCR7 predicts lung and lymphonodes metastasis (Zlotnik 2004). In contrast, in melanoma, CXCR4 is associated with pulmonary (Murakami et al. 2004, 2002) and liver metastasis, while CCR7 and CXCR3 is involved with lymphonodes metastasis (Monteagudo et al. 2007; Murakami et al. 2004; Takeuchi et al. 2004). In melanoma, CCR10 is linked with skin metastasis (Murakami et al. 2004), while CCR9 expression correlates with small intestine metastasis (Hwang 2004; Letsch et al. 2004). CX3CR1 expression drives perineural dissemination of human pancreatic ductal adenocarcinoma cells (Marchesi et al. 2008) and migration and survival of human prostate cancer cells (Shulby et al. 2004). Whereas the majority of current cancer therapies focus on the primary tumour, the identification of chemokines as key players in cancer metastasis formation have suggested these molecule as a target for the development of new therapeutics. The high number of different cancers expressing CXCR4 suggests the design of specific antagonists (e.g. CTCE-9908, AMD3100, peptides (T22, TN14003), antibodies, and small interfering RNA) all of which gave promising therapeutic results in a broad range of different preclinical cancer models. Further CTCE-9908, AMD3100, and MSX-122 are currently being tested in different phase I/II trials (Wong and Korz 2008).

COX-2

The cycloxygenase-1 and -2 (COX2) enzymes play a key role in the synthesis of lipid inflammatory mediators (prostaglandins and prostacyclines) from arachidonic acid and several studies have indicated that aberrant induction of COX2 and prostaglandins are implicated in the pathogenesis of various type of malignancies. Whereas mice genetically engineered to overexpress COX-2 in mammary glands, skin or stomach are more susceptible to develop tumours in these organs (Muller-Decker et al. 2002; Neufang et al. 2001; Oshima et al. 2004), COX2 deficient mice are more resistant to intestinal, skin and mammary tumourigenesis (Howe et al. 2005; Oshima et al. 1996; Tiano et al. 2002). These studies indicate that nonsteroidal anti-inflammatory drugs (NSAIDs) might be used for cancer prevention. Indeed the first study of colorectal cancer prevention based on sulindac administration was already performed in 1989 and it resulted in polyps elimination in four of seven familial adenomatous polyposis patients (Waddell et al. 1989). Next, several other clinical studies were performed in non-polyposis and high risk groups in order to test different doses of different COX-2 inhibitors (aspirin, sulindac, celecoxib, Rofecoxib) for both therapeutic and adverse effects (Baron et al. 2003, 2006; Bertagnolli et al. 2006; Giardiello et al. 1996, 2002; Higuchi et al. 2003; Sandler et al. 2003; Steinbach et al. 2000). These studies have highlighted that COX-2 inhibitors are able to suppress adenoma only at high dose, with a significant increased mortality from cardiovascular events. Hence NSAIDs somministration in the general population is not recommended and combination of NSAIDs with other chemoprevention agent should be considered.

In addition to therapeutic interventions targeting COX2, recent studies have identified polymorphisms in this molecule that could be used as a prognostic markers for patients with gastric and colorectal cancers (Kim et al. 2009; Pereira et al. 2009). Recent evidence have also demonstrated a positive correlation between COX2 expression in primary breast cancer with bone marrow micrometastasis suggesting that, in addition to colorectal tumours, COX2 inhibitors may be also useful in halting breast cancer progression and dissemination (Lucci et al. 2008).

NF-κB

The transcription factor NF-κB is a key orchestrator of innate immunity and inflammation and recent evidence suggest that this transcription factor represents a potential molecular bridge between inflammation and cancer (Karin 2006). Indeed, in innate immune, preneoplastic and malignant cells NF-κB drives the expression of inflammatory cytokines, adhesion molecules, angiogenic factors and enzymes, like COX-2 and iNOS, which are important for the synthesis of inflammatory mediators (PGE2 and NO respectively). Further, in cancer and epithelial cells exposed to carcinogens, NF-κB promote cell survival and proliferation through the activation of genes encoding for proteins important for cell cycle progression (e.g. cyclin D1, c-Myc) and anti-apoptotic pathway (cIAPs, A1/BFL1, BCL-2, c-FLIP). In innate immune and in various cancer cells NF-κB activation is promote by pro-inflammatory cytokines, such as TNF-α and IL-1, as well as by recognition of pathogen-associated molecular patterns. In cancer cells NF-κB can be also activated as a results of cell autonomous genetic alteration (amplification, mutations or deletions) (Courtois and Gilmore 2006).

Genetic studies targeting NF-κB activation in intestinal or in liver epithelial cells have demonstrated that this factor play a key role in inflammation-associated

cancer development (Greten et al. 2004; Pikarsky et al. 2004). Studies of colitis-associated cancer models in mice carrying tissue-specific gene targeting of NF-κB activation have unequivocally demonstrated the importance of inflammation driven by myeloid cells for colorectal cancer development (Greten et al. 2004). It should be noted that genetic targeting of NF-κB in liver epithelial cells can have divergent effect in different models of carcinogenesis, possibly dependent on the balance between promotion of either apoptosis or compensatory cell proliferation (Maeda et al. 2005; Pikarsky et al. 2004).

Whereas NF-κB activation in myeloid cells is associated with tumour promotion in inflammation-associated cancer models, in established tumours TAMs have delayed and defective NF-κB activation (Biswas et al. 2006). Experimental evidence indicate that accumulation of p50 NF-κB inhibitory homodimers in TAMs from murine fibrosarcoma and human ovarian carcinoma account for defective NF-κB activation as well as for the pro-tumour phenotype expressed by these cells (Saccani et al. 2006). Indeed ablation of p50 results in the restoration an M1 inflammatory response capable to inhibit both fibrosarcoma and melanoma tumours growth (Saccani et al. 2006). A recent study has showed that NF-κB activation plays a relevant role in governing macrophages polarization during different stage of tumour development (Hagemann et al. 2008).

HIF-1α

Hypoxia is a common feature of solid tumours that has been associated with decreased therapeutic response, malignant progression, local invasion and distant metastasis. The transcription factor hypoxia inducible factor 1 is the major regulator of cell adaptation to hypoxic stress, as well as the pivotal orchestrator of angiogenesis and tumour invasion. HIF-1alpha is upregulated in inflammatory conditions and accumulating evidence indicate interconnections and compensatory pathways between the NF-κB and HIF-1alpha systems (Rius et al. 2008).

Due to the central role of hypoxia in tumour promotion, HIF-1alpha activity in cancer cells represents a suitable prognostic marker for tumour progression (Mariani et al. 2009; Yohena et al. 2009) as well as a potential target for anticancer therapies (Giaccia et al. 2003). In this regards, a recent study has demonstrated that HIF-1alpha expression correlates with the metastatic phenotype of human gastric adenocarcinoma (Rohwer et al. 2009). HIF-1alpha expression is indeed mainly localized at the invading tumour edge while is almost absent in early gastric carcers. Further HIF-1-alpha-inhibitor 2-methoxy-estradiol significantly reduced metastatic properties of gastric cancer cells, suggesting a potential therapeutic benefit of HIF-1alpha inhibition for metastatic gastric cancer (Rohwer et al. 2009). Since the association between hypoxia and tumour cell radio- and chemo-resistance is known since a long time, the inhibition of HIF1-alpha could be an efficient strategy to improve the therapeutic effects of conventional radiation and cytotoxic drugs. Accordingly, using a human colon carcinoma cell line growth as three-dimensional spheroids (which is a model that more closely reproduces the hypoxic environment of solid tumours) Ravizza et al. (2009) have indeed demonstrated that HIF-1alpha ablation by siRNA prevents hypoxia-induced resistance to different cytoxic drugs and sensitises hypoxic cells to 5-fluorouracil-inducing apoptosis. In addition to strategies aimed at blocking HIF-1alpha accumulation or at promoting its degradation, different drugs against several key HIF transcriptional targets have been developed and approved for clinical use. Among these Bevacizumab, a monoclonal antibody against VEGFA, is currently used for the treatment of metastatic colorectal cancer (Hurwitz et al. 2004).

Despite several experimental evidence indicate that hypoxia contributes to tumour progression and spread, few studies suggest that hypoxia can also inhibit carcenogenesis. Using a multistage murine skin chemical carcinogenesis model, Scortegagna et al. (2009) have demonstrated that papilloma proliferation and their malignant conversion was significantly inhibited in HIF-1 gain of function transgenic mice as compared with their wild-type counterpart. Further, exposure of non-small cell lung cancer cells to hypoxia results in decreased production of soluble and membrane-bound complement inhibitors and consequently in enhancement of complement-mediated killing of cancer cells (Okroj et al. 2009).

STATs

The importance of STAT-6 activation in tumour-promoting function was suggested by studies performed with genetically modified mice. Indeed, TAM from STAT6-/- tumour-bearing mice displayed an M1 phenotype associated with immunologically rejection of spontaneous mammary carcinoma (Sinha et al. 2005).

STAT-3 is constitutively activated in several human cancer cells and tumour-associated leukocytes and it represents a point of convergence for several oncogenic signalling pathways (Yu et al. 2007).This transcription factor supports oncogenesis through different mechanisms ranging from the activation of genes crucial for proliferation and survival to the enhancement of angiogenesis and metastasis. The activation of STAT3 in tumour cells has been shown to increase the capacity

of tumours to evade the immune system by inhibiting the maturation of dentritic cells (Wang et al. 2004) and suppressing the immune response (Kortylewski et al. 2005). Recently, in a melanoma tumour model, authors emphasized the importance of STAT3 for tumour progression elucidating new molecular pathways important for STAT-3 immunosuppressive activity (Kortylewski et al. 2009). The authors have indeed demonstrated that STAT3 plays a divergent role in the modulation of IL-23 and IL-12, two related cytokines, which play opposite role in carcinogenesis. In particular, STAT3 inhibits anti-tumour IL-12p35 expression in dentritic cells while promoting the pro-carcinogenic IL-23 expression in tumour-associated macrophages (Kortylewski et al. 2009). Another study of colitis-associated tumourigenesis has highlighted the mechanisms underlying the link between STAT3 and inflammation (Bollrath et al. 2009). Using genetic modified mice carrying the intestinal epithelial-cell-specific STAT3 ablation or hyperactivation, they demonstrated a dual role for mucosal STAT3 in mediating an anti-inflammatory cytoprotective effect as well as in enhancing tumour growth (Bollrath et al. 2009).

Overall this evidence suggests STAT-3 as a molecular target for new anti-tumour drugs. In these regards, testing of different small molecule inhibitors of STAT3 activation in preclinical model of cancers has given promising results for their application as anti-tumour drugs (Costantino and Barlocco 2008; Heimberger and Priebe 2008).

Conclusions

Numerous experimental and clinical studies highlight the pro-tumoral activity of inflammation, while other evidence demonstrates that inflammation can support anti-tumour functions. This paradox may reflect specific circuits expressed within the tumour microenvironment. Recent evidence has suggested that, a dynamic M1 versus M2 change in polarized inflammation occurs during cancer progression. Whereas M1 macrophages promote tumour initiation and activate an adaptive immune response capable to eliminate nascent neoplastic cells (elimination phase), tumour progression (equilibrium phase) is paralleled by a gradual switching of macrophage polarization towards the M2 phenotype, which concurs to the establishment of permissive conditions for tumour growth and spread (escape phase). The gradual inhibition of NF-κB activity is associated with the M1 versus M2 switching of macrophage functions (Saccani et al. 2006) (Fig. 3). Strategies targeting this dynamic change in TAMs functions during different stages of cancer development may potentially represent a novel anticancer approach. Within this scenario, therapeutic efficacy of anti-NF-κB strategies against cancers may be subject to both tumour stage and polarization status of infiltrating leukocytes.

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