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Plasticity of Macrophage Function during Tumor Progression: Regulation by Distinct Molecular Mechanisms

Subhra K. Biswas,* Antonio Sica,† and Claire E. Lewis2‡

Recent studies have shown that macrophages play an important part in both tumor initiation and various key steps in growth and metastasis. These cells show a remarkable degree of plasticity during tumor development with a “switch” in macrophage phenotypes occurring during the course of tumor progression. During chronic inflammation they appear to predispose a given tissue to tumor initiation by the release of factors that promote neoplastic transformation. Following this, their phenotype shifts more toward one that is immunosuppressive and supports tumor growth, angiogenesis, and metastasis. In this review, we discuss the evidence for this plasticity of macrophage functions, the specific signaling mechanisms that may be regulating it, and the new targets for anticancer therapies highlighted by these findings. The Journal of Immunology, 2008, 180: 2011–2017.

While a number of early studies have reported the formation of malignant tumors at sites of chronic inflammation and inferred a link between inflammation and cancer, recent studies using transgenic mouse models have provided definitive evidence for this (1–3). One particular inflammatory cell, the macrophage, has emerged as a central regulator of both tumor onset and progression (4). Proinflammatory macrophages at sites of chronic inflammation appear to contribute to neoplastic transformation, whereas macrophages in established tumors support tumor growth, angiogenesis, and metastasis (5, 6).

Two distinct polarization states have been described for macrophages: the M1 (or classically activated) and M2 (or type II alternatively activated) macrophage (7). The M1 phenotype is proinflammatory and characterized by the release of inflammatory cytokines, reactive nitrogen intermediates (RNI), reactive oxygen intermediates (ROI), and microbicidal/tumoricidal activity. M2 macrophages, in contrast, are polarized by anti-inflammatory molecules like IL-4, IL-13, and IL-10, apoptotic cells, and immune complexes to show an immunosuppressive phenotype and an enhanced release of anti-inflammatory cytokines, scavenging potential, and ability to support angiogenesis, tissue remodeling, and repair.

A number of studies have shown that the macrophages present in malignant tumors, so-called tumor-associated macrophages (TAM), exhibit predominantly an M2-like phenotype (8–10). However, there is now growing evidence for the phenotype of macrophages being dependent on the stage of tumor development, with the display of a tumorogenic, M1-like phenotype in sites of chronic inflammation where tumors develop and a tumor-promoting, M2-like one in established tumors.

Plasticity and divergent macrophage phenotypes in tumors

Macrophages and tumor initiation. As mentioned previously, epidemiological and clinical studies have shown that various chronic inflammatory diseases predispose patients to the risk of cancer at the same site (3, 11, 12). For example, there is an increased risk of colorectal cancer in patients with Crohn’s disease or ulcerative colitis, pancreatic cancer in patients with chronic pancreatitis, gastric carcinoma following infection with Helicobacter pylori, and nasopharyngeal cancer following Epstein-Barr Virus infection (3, 12).

Investigations of the link between inflammation and these forms of cancer have suggested a central role for macrophages in tumor onset at these sites (3, 11). It is believed that macrophages, through their persistent inflammatory phenotype during chronic inflammation, release cytotoxic molecules like RNI, ROI, and migration inhibitory factor that cause extensive tissue damage, DNA damage/mutation, and defective p53 activity in the surrounding epithelial cells, predisposing them to neoplastic transformation.

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premalignant transformation and tumor initiation (3, 11) (Fig. 1, left panel). Further, the production of cytokines like TNF-α, IL-1β, and IL-6 by TAM provide prosurvival signals for these premalignant cells, supporting tumorigenesis (12, 13) (Fig. 1, left panel). Indeed, studies of murine models of colitis-induced premalignant cells, supporting tumorigenesis (12, 13) (Fig. 1, left panel). This conforms to the definition of the immunosuppressive M2 macrophage phenotype (7). Expression of typical M2 markers like arginase-I, YM1,Fizz1, and MGL2 has also been observed in TAM from both murine fibrosarcoma and BW-Sp3 T-lymphoma (9, 20). An immunosuppressive phenotype for TAM has also been noted in some forms of human tumor. For example, TAM are highly proangiogenic in poorly vascularized/necrotic tumor areas in response to the hypoxia present (26). Moreover, their density in these sites positively correlates with tumor angiogenesis in breast tumors (27). By contrast, high numbers of TAM in close proximity to large, well vascularized areas of tumor cells correlate with a good prognosis in some human tumors, suggesting a possible antitumor (M1-like) phenotype at these sites (28).

“Mixed” or overlapping functional phenotypes in TAM. The functions of TAM appear to vary according to their location in tumors, presumably in response to local signals (24). For example, TAM are highly proangiogenic in poorly vascularized/necrotic tumor areas in response to the hypoxia present (26). Moreover, their density in these sites positively correlates with tumor angiogenesis in breast tumors (27). By contrast, high numbers of TAM in close proximity to large, well vascularized areas of tumor cells correlate with a good prognosis in some human tumors, suggesting a possible antitumor (M1-like) phenotype at these sites (28).

Furthermore, evidence also exists for TAM expressing both proinflammatory (M1-like) and immunosuppressive (M2-like) characteristics and thus a “mixed” phenotype in some forms...
of established tumors. Classically, proinflammatory (M1) macrophages express inducible NO synthase (iNOS) and metabolize arginine by releasing NO (or RNI) and citrulline, whereas immunosuppressive (M2) macrophages up-regulate arginase (I and II) to metabolize arginine into urea and L-ornithine (29). Interestingly, in some mouse tumor models TAM express high levels of both iNOS and arginase-1 simultaneously (30, 31). TAM from murine fibrosarcoma, which otherwise show a M2 phenotype, also express proinflammatory Th1 chemokines like CCL5, CXCL9, and CXCL10 (9). Similarly in humans, monocytes from advanced stage gastric cancer patients express higher levels of both the inflammatory cytokine IL-12 and the anti-inflammatory cytokine IL-10 than monocytes from healthy donors (32). Human macrophages cocultured with ovarian carcinoma cell lines show high levels of both proinflammatory and anti-inflammatory cytokines like TNF-α, IL-18, TGFβ1, and CCL22 together with M2 markers like mannose receptor and scavenger receptor (33). Together, the above findings suggest the existence of a “mixed” macrophage phenotype in tumors.

A recent study by Auffray et al. (34) shows that the phenotype of macrophages can change fairly rapidly from an M1 to an M2 phenotype in vivo. They found that a subset of Gr1+CX3CR1high monocytes “patrol” inside blood vessels and extravasate into inflamed tissues where they differentiate into macrophages and release proinflammatory cytokines (TNF-α and IL-1β) during 1–2 h of Listeria monocytogenes infection. At later time points (8 h) these cells cease this function and start to express markers of an M2 phenotype: arginase I, FIZZ1, Mgl2, and mannose receptors.

Molecular mechanisms regulating such a “shift” in macrophage phenotype

The multifaceted role of NF-κB. NF-κB is one of the most crucial transcription factors regulating the inflammatory repertoire of macrophages, particularly their expression of proinflammatory cytokines, costimulatory molecules, and other activation markers in response to diverse environmental cues (e.g., stress signals, inflammatory cytokines, pathogens, and hypoxia) (Fig. 2) (13). As shown in Fig. 2, NF-κB activation is largely regulated through activation of the inhibitor of κB kinase (IKK) trimeric complex that consists of two kinases, IKKα and IKKβ, and a regulatory protein, IKKγ (or NEMO). Classical NF-κB signaling principally involves the activation of IKKβ, which triggers further downstream events involving the phosphorylation-mediated degradation of the inhibitory molecule I-κB, releasing the p65/p50 NF-κB heterodimer from the NF-κB/I-κB complex for its nuclear translocation to trigger inflammatory gene transcription.

The contribution of NF-κB to tumor progression has been recently dissected in mouse cancer models for liver, colon (13–16), and chemically induced fibrosarcoma (9, 10). In brief, these studies indicate that macrophage NF-κB activation varies depending on the stage of the tumor growth. NF-κB is activated in macrophages during early stages of tumor initiation but is defective in established tumors. For example, in dextran sodium sulfate-induced colitis-associated colorectal cancer (26), myeloid cell-specific targeting of IKKβ was seen to result in decreased premalignant enterocyte proliferation and reduced tumor number and size (Fig. 3). It was proposed that oral administration of dextran sodium sulfate disrupted the intestinal endothelial lining, exposing the lamina propria macrophages to activation by enteric bacteria and triggering NF-κB activation in these cells. This leads to their release of a variety of inflammatory products (including the cytotoxic reactive species RNI and ROI) that not only initiate enterocyte transformation but also supports the growth of these cells through the release of mitogenic cytokines like IL-6.

A similar study by Maeda et al. (15) of diethylnitrosamine (DEN)-induced hepatocellular carcinoma (HCC) showed that
specific ablation of IKKβ in Kupffer cells caused down-regulation of inflammatory cytokines like IL-6 and TNF-α and hematotitogens needed for the growth and survival of tumor cells, resulting in a marked reduction in tumor load. By contrast, IKKβ deletion in DEN-treated premalignant hepatocytes sensitized them to increased cell death (apoptosis and necrosis), leading to compensatory proliferation of the initiated cells and increased tumor load (Fig. 3). This was possibly due to the fact that the detection of necrotic hepatocytes by Kupffer cells (liver macrophages) triggered their activation, resulting in secretion of cytokines and growth factors supporting hepatocyte regeneration (13). Luedde et al. (35) also showed that hepatocyte-specific deletion of NF-κB NEMO (Fig. 2) in hepatocytes triggered increased apoptosis and that these apoptotic bodies triggered resident macrophages (Kupffer cells) to secrete elevated inflammatory cytokine release (Fig. 3). Chronic exposure to these cytokines together with high ROI and JNK activity in the hepatocytes (due to the absence of NEMO/NF-κB activity) predisposed them to malignancy. However, the role of apoptotic vs necrotic debris in macrophage/TAM polarization is still unclear. Apparently, macrophages exposed to apoptotic cell debris have impaired NF-κB activity and express high TGF-β, correlating with an immunosuppressive phenotype, whereas necrotic debris induces expression of proinflammatory mediators (36).

In contrast to the role of NF-κB in macrophages during early stages of tumor initiation and growth (1, 13), we recently demonstrated defective NF-κB function in TAM from established chemically induced murine fibrosarcomas (9, 10). Defective NF-κB activation was attributed to the overexpression of nuclear p50 NF-κB homodimers which inhibits the transcription of proinflammatory cytokines like IL-12p40, TNF-α (Fig. 1, right panel, diagram A) (10). Interestingly, depletion of p50 using a p50−/− mice re-instate an inflammatory (M1) phenotype in TAM and reduced tumor growth. The reasons for overexpression of p50 NF-κB are not yet evident, although IL-10 appears to participate in this. Interestingly, endotoxin-tolerant monocytes, which display a similar phenotype as TAM (defective TNF-α/high IL-10) also express high levels of p50 NFκB homodimers (37).

It is interesting to compare the role of NF-κB activation in TAM and tumor cells. In the latter it leads to diverse consequences, the expression of inflammatory cytokines, proangiogenic growth factors and, most importantly, expression of antiapoptotic genes. Greten and colleagues (14) showed that in their colitis-associated colorectal cancer model, deletion of IKKβ in enterocytes causes a reduction in the number of tumors but no change in tumor size. This was due to increased apoptosis of the premalignant enterocytes in the absence of NF-κB activation (14) (Fig. 3). Similar observations from the Mdr2−/−ΔN-IκBα transgenic mice, where hepatitis (hep) is followed by HCC, showed that conditional deletion of NF-κB in hepatocytes (through the nondegradable IκB super-repressor) significantly reduced tumor onset due to profound hepatocyte apoptosis mediated by the inhibition of NF-κB-inducible anti-apoptotic genes like Bcl-xL and GADD45β (Fig. 3) (16). A role for Kupffer cell-derived TNF-α in mediating the NF-κB activation in these malignant hepatocytes was also suggested (Fig. 3).

Role of Toll-like receptors. TLR/IL-1R signaling is an important upstream component of NF-κB activation in macrophages (12, 13). In inflammation-induced cancers, activation of TLR/IL-1R on stromal macrophages may be triggered by: 1) direct interaction with bacteria at sites of chronic infection (e.g., enteric bacteria in colitis-associated colon cancer or H. pylori gastric cancer) (12, 14); or 2) interaction with tumor-cell-derived proinflammatory cytokines like IL-1; and/or 3) recognition of components of necrotic tumor cell debris like HMGB1 (high mobility group box 1) or S100 (1, 13, 38). However, TLR/IL-1R signaling is not exclusive to stromal cells, as tumor cells also possess a functional TLR/IL-1R pathway.

TLR4 activation on human lung cancer cells promotes production of the immunosuppressive cytokine TGFβ and the proangiogenic factors VEGF and CXCL8 as well as confer resistance to TNF-α-induced apoptosis and tumor cell survival (39). In a H22 tumor model and B16 melanoma, L. monocytogenes was reported to promote tumor growth via tumor cell TLR2 signaling, which stimulated tumor cell proliferation through iNOS and IL-6 production (40). Similarly in the K19-C2mE murine gastric cancer model, the interaction of gastric bacterial flora with TLR4 was shown to trigger TNF-α by tumor cells, which activated mucosal macrophages (38).

Chronic activation of TLRs in conjunction with other receptors on TAM by tumor cell-derived substances like hyaluronan (HA) fragments (41) or heat shock proteins (HSP) (42) can render them
immunosuppressive (Fig. 1, right panel, diagram B). HA signals through the CD44 receptor on human monocytes, inducing an M2 phenotype. High levels of HA were detected in the supernatants of human hepatoma cells (SK-Hep1) as well as glioma cells (U251) and were shown to be responsible for the polarization of human monocytes to a IL-12lowIL-10high M2 phenotype when cocultured with these tumor cells (41). This phenotype was correlated to that of human TAM from HCC. Biochemical analysis revealed CD44 as the receptor responsible for the HA signaling in human monocytes (41).

A preferential role of TLR2 activation in triggering an M2-like cytokine profile (IL-12lowIL-10high) in dendritic cells and macrophages through ERK/MAPK phosphorylation has been reported (43). Biochemical studies show a direct role for TPL2 (tumor progression locus 2)-mediated ERK activation in triggering IL-10 expression in TLR4-activated macrophages (44) (Fig. 2). Endogenous ligands to TLR2 and TLR4 such as HA and heat shock protein 60 are abundantly found in malignant tumors (41, 42), so the activation of the TPL2-ERK pathway may be involved in shaping the immunosuppressive phenotype of TAM. Moreover, the phagocytosis of apoptotic tumor cells by human macrophages is also known to inhibit LPS/TLR4-induced expression of TNF-α and IL-6, but not IL-10 expression, suggesting another possible pathway for macrophage polarization in tumors (45).

**The Tie-2/Ang-2 pathway.** As mentioned previously, Tie-2-expressing monocytes (TEM) exist in human and murine tumors (24, 25). Endothelial cells as well as tumor cells are known to up-regulate Ang-2, a ligand for Tie-2 in tumors (46). Our recent data suggest that tumor-derived Ang-2 may facilitate the recruitment of Tie-2+ monocytes/macrophages into tumors (Fig. 1, right panel, diagram C) (46). Importantly, Ang-2 also significantly inhibits the release of proinflammatory cytokines like TNF-α and IL-12 by Tie-2+ monocytes in vitro (Fig. 1, right panel), an effect more pronounced in hypoxia (46). These findings suggest that the Ang-2/Tie-2 axis may represent another potential mechanism for dampening the angiogenic phenotype and prompting the immunosuppressive phenotype of TAM, especially in hypoxic areas of tumors. In human endothelial cells, Ang-1/Tie-2 has been shown to inhibit NF-κB activation through the interaction of Tie-2 to the negative regulator, the A20-binding inhibitor of NF-κB activation (ABIN-2) (47). In a study on non-small lung cancer, it has been proposed that tumor-produced IL-10 promotes stromal vascularization through expression of Ang-1, Ang-2, and Tie-2 (48). Further studies are now needed to clarify the role of NF-κB and other signaling pathways in mediating the effects of Ang-2 on Tie-2-expressing monocytes.

**The TRIF/TBK1/IRF3 pathway.** Preferential activation of the TRIF-dependent IRF3/STAT1 pathway (where TRIF is TLR/IL-1R domain-containing adaptor inducing IFN-β, TBK is TANK-binding kinase, and IRF is IFN regulatory factor) has been demonstrated in TAM in murine fibrosarcoma (Fig. 2) (9). This was evident from the constitutive activation of STAT1 and the up-regulation of type I IFN-inducible genes like CCL5, CXCL9, and CXCL10 in the TAM under basal and LPS-activated conditions (Fig. 1, right panel). Recently, IL-10 transcription has been shown to be regulated by the TRIF/IRF3 pathway via TRAF3 and type I IFNs (49) (Fig. 2). Thus, a functional TRIF/IRF3/STAT1 pathway in the fibrosarcoma TAM may explain the high IL-10 expression in these cells. Further, the significance of STAT1 in protumoral circuits and especially in TAM is evident from: 1) the observation that STAT1−/− TAM failed to induce the T cell suppression evoked by STAT1-expressing TAM (30); 2) resistance of STAT1−/− mice to tumor induction by methylcholanthrene (50); and 3) the enhanced efficacy of IL-12 to cause regression of murine squamous cell carcinoma in STAT1−/− mice (29). However, further investigations of the TRIF/IRF3/STAT1 pathway in TAM from different tumor models will be needed to understand its significance in tumor progression.

The TRIF/IRF3 pathway is also active in tumor cells. Transfection of HEK293 cells with TRIF pathway members TBK1 and IRF3 was demonstrated to support angiogenesis through the release of CXCL8, CCL5, and VEGF (51). In fact, high TBK1 expression has been found in human breast and colon tumors where it may be up-regulated, in part, by tumor hypoxia. Interestingly, the antiangiogenic chemokines CXCL9 and CXCL10 (52) are also downstream target genes for the TRIF/TBK1/IRF3 pathway (Fig. 2) (9). Thus, it is possible that this pathway, through differential modulation of both proangiogenic and antiangiogenic chemokines, may play an integral role in fine-tuning tumor angiogenesis. These aspects are under further investigation (A. Sica, unpublished data).

Taken together, it is apparent that TRIF pathway members like TBK1 and IRF3 could play a role in mediating the proeffects of TAM and, as such, may represent a potential therapeutic target.

**Hypoxia-induced pathways.** Hypoxia has profound effects on macrophage functions including their migration into tumors and patterns of gene expression, especially those encoding proangiogenic cytokines and enzymes (Fig. 1, right panel) (53). Hypoxia induces gene expression in these cells through up-regulation of the transcription factors hypoxia-inducible factors (HIF) 1 and 2 (HIF-1 and HIF-2). Macrophages up-regulate both HIFs and subsequently a wide array of HIF target genes in hypoxic/necrotic areas of human tumors (53). Most importantly, hypoxia is a potent inducer of both VEGF and MMP7 in TAM, both of which are known to support tumor angiogenesis, invasion, and metastasis (Fig. 1, right panel, diagram D). In addition, hypoxia up-regulates the expression of M2 macrophage markers like IL-10, arginase, and PGE2. It also modulates expression of proinflammatory genes like TNF-α, IL-1, migration inhibitory factor (MIF), CCL3, and COX2 (53). Recently, a crucial role for HIF-1α in the differentiation, phagocytic activity, and inflammatory responses of macrophages has been reported (54). These findings suggest that TAM diversity may be driven at least in part by their location within the tumors and proximity to signals like hypoxia.

**Targeting the tumor-promoting functions of TAM**

As evidence emerges for the nature of the signaling pathways involved in the onset of the tumor-promoting (M2-like) phenotype of TAM, new and more sophisticated approaches are being taken to “re-educate” these cells to express a more anti-tumor, M1-like phenotype. One possible “druggable” target may be overturning the suppression of NF-κB that occurs in TAM after tumor initiation. As mentioned earlier, our own studies using p50−/− mice (11) have shown that the enhancement of NF-κB activity in TAM in established tumors helps to “rescue” their immunosuppressive and antitumor functions. One way to
achieve this in patients might be the ex vivo expansion and transplantation of autologous hemopoietic stem cells transduced with a lentiviral vector encoding a construct overexpressing p65 NF-κB or p50 NF-κB siRNA under the control of a macrophage-specific promoter like c-fms or CD68. This approach has been used for gene therapy in apolipoprotein E (ApoE)/−/− mice (55). ApoE/−/− bone marrow cells were transduced with the lentiviral vector encoding the human ApoE gene (under the control of a macrophage-specific synthetic promoter) and used to transplant ApoE/−/− mice. Macrophage expression of ApoE from 10 to 20 wk of age significantly reduced atherosclerotic lesions in recipient ApoE/−/− mice. Alternatively, monocytes from the bloodstream could be lentivirally transduced to express p65 NFκB or p50 NF-κB siRNA and reintroduced into the patient. The mode of delivery of such genetically engineered cells would depend on the type of tumor and could include i.p. injection in advanced ovarian carcinoma patients (to target their peritoneal metastases) or intrahepatic arterial delivery in liver cancer patients. Introduction of conditionally inducible constructs that are “turned on” in TAM by tumor hypoxia or by the injection of a particular drug may help to enhance the level of temporal and site-specific control of therapeutic gene expression.

Alternatively, a combination of CpG oligodeoxynucleotides and an IL-10 receptor-specific Ab has been shown recently to reinstate NF-κB activation specifically in TAM and concomitantly activate an increased antitumor repertoire in these cells. This led to the debulking of large tumors within 16 h of in vivo administration of the agents (56). CpG oligonucleotides induced NF-κB activation through the triggering of TLR9 signaling in TAM (Fig. 2), and the co-use of an IL-10 receptor Ab reduced IL-10 signaling in TAM, thereby reducing their M2 polarization.

It should be noted though that given the evidence described previously for M1-like macrophages playing a part in tumor onset, the use of strategies to reorientate TAM toward an M1 phenotype (e.g., by reactivating NF-κB) could, in theory, reintroduce tumorigenic TAM into the body (2, 13). However, the other tumorigenic signals present in chronic inflammatory lesions when macrophages exhibit this tumorigenic M1-like role are absent in established tumors. Moreover, the longevity of most forms of NF-κB-activating approaches in TAM would be shorter lived than the sustained M1 functions seen in chronically inflamed tissues (1). This may reduce the risk of secondary cancer development resulting from such NF-κB-based therapies.

The significant level of TAM migration into hypoxic areas of tumors could be exploited so that these cells are used to target genes to these otherwise inaccessible (i.e., poorly vascularized) sites in tumors. In such a cell-based gene therapy approach, the therapeutic gene is placed under the control of a hypoxia-activated promoter sequence in the macrophage, thereby restricting its expression to TAM in hypoxic area of tumors (57).

Because specific subsets of TAM appear to decrease the efficacy of established anticancer treatments like antiangiogenic therapy, focus is now being placed on targeting these subsets before or during such treatments. For example, the refractoriness of tumors to treatment with an VEGF Ab has recently been attributed to tumor-infiltrating CD11b+Gr1+ myeloid cells (58) a subset of which may be macrophages. Similarly, an Ab against the VEGF homologue, placental growth factor (PIGF), inhibits the growth and metastasis of various tumors, including those resistant to VEGFR inhibitors, and enhances the efficacy of chemotherapy (e.g., cyclophosphamide and gemcitabine) (59). One of the mechanisms for the enhanced efficacy of this approach is thought to be its ability to prevent infiltration of TAM and thus ablate the angiogenic rescue mounted by these cells in treated tumors. Furthermore, a recent study has also demonstrated a possible role for TAM in promoting radioresistance in tumors (60).

Concluding Remarks

An interesting picture has now emerged for the plasticity of macrophage function playing a crucial role in both the onset and progression of malignant tumors. Tumorigenesis appears to involve a proinflammatory phenotype in macrophages that, through the chronic release of inflammatory mediators, drives damaged epithelial cells toward neoplastic transformation. Once the tumor is established, however, TAM assume an immunosuppressive phenotype and carry out a number of potent tumor-promoting functions (29) (Fig. 1). The NF-κB pathway appears to be central in this phenotype switching of macrophages during tumor progression, and strategies to target this and related molecular pathways in TAM during different stages of tumor growth are now being developed.

Disclosures

The authors have no financial conflict of interest.

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