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Epithelial-mesenchymal transition and inflammation at the site of the primary tumor

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Abstract

Tumor growth and progression are the products of complex signaling networks between different cell types within the tumor and its surrounding stroma. In particular, established tumors are known to stimulate an inflammatory reaction via the secretion of cytokines, chemokines, and growth factors that favor the recruitment of a range of infiltrating immune cell populations into the tumor microenvironment. While potentially able to exert tumor control, this inflammatory reaction is typically seized upon by the tumor to promote its own growth and progression towards metastasis. This review focuses on recent advances in understanding how an established tumor can initiate an inflammatory response via the release of pro-inflammatory mediators, such as IL-6 and IL-8, and their roles in cancer metastasis. In particular, the role of the epithelial-mesenchymal transition (EMT), a phenotypic switch observed in carcinomas that promotes progression towards metastasis, is discussed here in relation to cancer inflammation.

Keywords

IL-8; IL-6; EMT; inflammation

Introduction

The connection between inflammation and cancer has been long recognized [1]. Multiple lines of evidence now support the idea that this connection is two-fold, whereby a chronic inflammatory response resulting from certain autoimmune diseases [2–4] or chronic infections [5] could lead to cancer and, in turn, an established tumor could stimulate an inflammatory reaction that leads to the recruitment of a range of immune-infiltrating cell populations into the tumor microenvironment (TME). Ultimately, the link between cancer and inflammation involves a series of complex and dynamic signaling networks established between different cellular components of the tumor mass, via the activity of a range of

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soluble immune-mediators, including cytokines, chemokines and growth factors. The type and level of inflammatory mediator(s) accumulated at the site of the tumor will define the type and range of infiltration of immune cells, which may include macrophages, neutrophils, myeloid-derived suppressor cells (MDSCs) and natural killer (NK) cells of the innate arm of the immune system, or B and T lymphocytes of the adaptive immune system. While the resulting immune infiltrate could mediate an anti-tumor response, the inflammatory response is typically seized upon by the tumor to promote its own growth and progression towards metastasis.

This review is focused on recent advances in understanding how an established tumor can lead to an inflammatory microenvironment that, in turn, could promote tumor dissemination and resistance to therapies, which are two central features of metastatic disease. In particular, the role of the phenomenon of epithelial-mesenchymal transition (EMT), a phenotypic switch observed with carcinomas that promotes progression towards metastasis, is discussed here in relation to cancer inflammation.

Tumor-driven inflammation: key soluble immune-mediators

A central feature of a tumor-initiated inflammatory response is the ability of the cancer cells to release and promote the accumulation of inflammatory soluble factors in the surrounding stroma, which ultimately facilitate the recruitment of different leukocytes and lymphocytes from circulation. Two well-characterized inflammatory mediators in this regard are the cytokine interleukin-6 (IL-6) and the chemokine IL-8.

IL-6 is an inflammatory cytokine commonly produced in response to infection, tissue trauma or stress following, for example, exposure to UV or ionizing radiation [6]. Initially discovered for its capacity to promote the maturation of B cells [7, 8], recent advances in understanding IL-6 signaling have revealed a central role for this cytokine in both innate and adaptive immunity [9]. In cancer, IL-6 is one of the most abundant cytokines in the TME, and its overexpression has been reported in multiple tumor types, including non-small cell lung [10], pancreatic [11], colon [12], breast [13], prostate [14] and ovarian carcinomas [15], hematological malignancies [16], and melanoma [17]. The sources of IL-6 found at the tumor site include the cancer cells and/or infiltrating immune cell populations such as tumor-associated macrophages (TAMs) [18], T cells [19], and others. Once secreted, IL-6 signaling depends upon its binding to a specific IL-6 receptor (IL-6R) and the subsequent binding of the IL-6/IL-6R complex with glycoprotein 130 (gp130), resulting in an activated receptor complex [20]. This receptor complex then regulates the Janus kinase-signal transducer and activator of transcription 3 (STAT3) pathway, as well as other signaling pathways [21, 22]. Activation of the IL-6/STAT3 pathway has been shown to result into a range of tumor-promoting effects, including (a) stimulation of cancer cell proliferation via direct control of cell cycle-associated proteins [23]; (b) activation of tumor cell survival pathways that could contribute to resistance to anti-cancer therapeutics [24]; (c) induction of tumor EMT which, as indicated below, could facilitate tumor migration and invasiveness and enhance metastatic dissemination; and (d) modulation of infiltrating immune cells by directly affecting the differentiation of myeloid cells [25]. Attesting to the tumor-promoting effect of this inflammatory cytokine, high levels of serum IL-6 have been associated with

poor patient clinical outcome [26] and with resistance to therapies [27] in various tumor types.

The pro-inflammatory chemokine IL-8 (CXCL8) was initially identified for its role in the chemo-attraction and degranulation of neutrophils at the site of infection or inflammation [28]. In normal physiology, IL-8 is secreted by macrophages, endothelial cells, or epithelial cells in response to infection or tissue injury [29]. The biological effects of IL-8 are mediated via binding with two G protein-coupled receptors, cysteine-X-cysteine chemokine receptor-1 (CXCR1, IL-8R α) or -2 (CXCR2, IL-8R β), which are normally expressed on neutrophils, monocytes and endothelial cells [30]. The chemokine IL-8 plays a crucial role in the resolution of inflammation and tissue repair by promoting the recruitment of phagocytes to the site of tissue injury or infection, as well as through the proliferation, survival, and migration of endothelial cells [31]. Aberrant expression of IL-8 is observed in various chronic inflammatory conditions, including psoriasis [32], inflammatory bowel disease [33], and others. In cancer, abnormal over-expression of IL-8 has been reported for a range of human tumors, including solid carcinomas of breast, prostate, ovarian, hepatocellular, colon, lung and pancreatic origin [34–37], and in various hematological malignancies [38]. There are several potential sources of IL-8 found at the tumor site, including cancer cells, endothelial cells, tumor-associated fibroblasts and immune-infiltrating cells. Multiple studies have now demonstrated that IL-8 can function in a paracrine or autocrine manner to affect the various cellular components of the TME. Functioning in a paracrine manner, for example, IL-8 released by cancer cells has been shown to promote the recruitment of various immune cell populations, mainly macrophages, neutrophils and suppressor cells of myeloid origin (see below), as well as to stimulate the angiogenic response in vascular endothelial cells leading to the formation of new blood vessels [39]. In addition, IL-8 released by tumor cells can function in an autocrine fashion to induce carcinoma cells to acquire a mesenchymal-like phenotype (i.e., induction of an EMT), as described in detail below. In support of a role of the IL-8/IL-8R axis in cancer progression, high levels of serum IL-8 have been positively correlated with poor clinical outcome in patients with various types of tumors [34].

Tumor-driven inflammation: key inflammatory cell populations

Neutrophils

As the most abundant leukocytes in circulation, neutrophils are known as the “first responder” cells of the innate immune system [40], which are attracted to the site of an infection or inflammation where they mediate microbial clearance or tissue repair via phagocytosis and secretion of a range of cytokines, reactive oxygen species (ROS), and the antibacterial defensin peptides [41]. Recent studies have also shown that neutrophil infiltration can be substantial at the site of a primary tumor, where the degree of infiltration has been positively correlated with tumor grade in gliomas [42] and pancreatic cancer [43], and with poor prognosis in patients with hepatocellular, colorectal, head and neck squamous cancer, and others [44, 45]. In response to the presence of soluble immune-mediators at the tumor site, these tumor-associated neutrophils (termed TANs) acquire either anti-tumoral or

pro-tumoral functions, depending on their polarization towards a TAN1 vs. TAN2 phenotype, respectively [46].

A major chemoattractant for neutrophils at the tumor site is the chemokine IL-8, which acts via binding to the IL-8 receptors expressed on the surface of neutrophils. Utilizing inflammation-driven and spontaneous mouse models of intestinal and skin carcinogenesis, Jamieson and colleagues demonstrated that CXCR2 deficiency attenuated neutrophil recruitment to the tumor site, while reducing spontaneous tumorigenesis or suppressing the growth of established tumors [47]. Similar results were observed with a xenograft model of lung cancer [48] where tumor infiltration with neutrophils was significantly reduced by CXCR2 blockade or CXCR2 deficiency, which was also associated with reduced tumor growth.

Macrophages

An additional cell population of the innate arm of the immune system that influences the TME is macrophages. Originating from circulating monocytes that differentiate in response to tissue damage or infection, macrophages normally contribute to host defense by engulfing apoptotic cells and pathogens. Once recruited to the sites of infection or inflammation, macrophages can acquire different functional phenotypes in response to distinct external signals; the classical M1 type is achieved in response to IFN- γ or bacteria-derived products, such as LPS, while the alternative M2 type is cued by IL-4 and IL-13 [49, 50]. Classically activated M1 macrophages are highly phagocytic and participate in the induction of Th1 responses through the secretion of reactive oxygen species, nitrogen intermediates and inflammatory cytokines (IL-1, IL-6, IL-12, TNF). In contrast, M2 macrophages induce Th2 responses and are involved in resolution of inflammation via secretion of anti-inflammatory cytokines [50].

In malignant tissues, TAMs constitute the most abundant cell type of the leukocyte infiltrate of the TME, where they are capable of exhibiting either anti- or pro-tumor functions [51]. The analysis of murine and human tumors, however, demonstrates that TAMs are typically polarized towards a M2-like phenotype. These M2-like TAMs function as a pro-tumor cell type in the TME by mediating tumor growth, angiogenesis, and the suppression of adaptive immune responses [52]. Although the exact signals that promote a preferential M2-like activation of macrophages at the tumor site are not fully understood, it is believed that signals delivered by the tumor cells or other immune infiltrates, including IL-10, TGF- β and lactic acid, among others, could play a major role [53–55].

The ability of TAMs to promote cancer growth and maintenance has been shown for multiple cancer types, including pancreatic [56], glioma [57], and ovarian [58]. For example, Chen *et al.*, explored the role of TAMs in NSCLC patient samples and identified the relationship between IL-8 expression, TAMs, and patient survival. In the study, the density of TAM infiltration was shown to have a positive correlation with IL-8 expression and intratumoral microvessel counts, coupled with a negative correlation with patient survival [59]. Interestingly, a study from Sousa and colleagues [60] demonstrated not only the correlation between M2 TAMs and poor patient status in breast cancer patients, but also

found that breast cancer cells can ‘educate’ macrophages towards an immunosuppressive phenotype via the secretion of various cytokines.

Myeloid-derived suppressor cells (MDSCs)

Classically, myeloid progenitor cells migrate to peripheral organs from the bone marrow and give rise to differentiated macrophages, dendritic cells, and granulocytes. In tumors, however, a diverse population of immature immunosuppressive cells consisting of precursors and progenitors of myeloid cells, termed myeloid-derived suppressor cells (MDSCs), has been observed. In mice [61] and humans [62], MDSCs can be divided into two subgroups, granulocytic and monocytic, both of which exhibit suppressive activity on T-cell proliferation and activation. Human granulocytic and monocytic MDSCs are defined as CD33+ CD11b+ HLA-DR-/low CD15+ and CD33+ CD11b+ HLA-DR-/low CD14+, respectively. Elevated circulating levels of MDSCs have been reported in a range of human tumor types, and have been linked to poor prognosis in patients with melanoma [63]. Similar to other immune cells in the TME, MDSCs can be recruited and expanded within the TME by tumor cells via the secretion of soluble mediators. For example, a recent report demonstrated the chemo-attractant ability of IL-8 to recruit granulocytic and monocytic MDSCs isolated from the peripheral blood of healthy donors and advanced cancer patients [64]. Moreover, a significant correlation was observed between the levels of circulating MDSCs and the concentration of serum IL-6 and IL-8 in prostate cancer patients, and both cytokines correlated with clinical stage and poor prognosis [65]. In preclinical studies, Highfill and colleagues demonstrated a substantial expansion of CXCR2+ MDSCs in a murine model of rhabdomyosarcoma, which was significantly prevented by CXCR2 blockade or tumor implantation into CXCR2-deficient mice. Blockade of CXCR2 signaling was also shown to improve the anti-tumor effect of programmed death 1 (PD1) checkpoint blockade, attributed to the alleviation of the immunosuppressive environment originated by the MDSC infiltrate [66]. These studies provided evidence for the role of CXCR2 and its ligands in an inflammatory response that favors the recruitment of immune suppressive MDSCs to the tumor site.

Oncogenic signaling and tumor-driven inflammation

Perhaps one of the most studied mechanisms of tumor-initiated inflammation relates to the ability of certain oncogenes to trigger a cellular cascade that favors the secretion of soluble factors responsible for the inflammatory response, including IL-6 and IL-8, among others. One such oncogene is RAS, a family of small guanosine triphosphatases (GTPases) composed of N-, H-, and K-RAS that are constitutively activated in a range of human cancers via gain-of-function mutations. Constitutively activated RAS signaling is known not only to result into cell transformation, but also to facilitate the remodeling of the TME to promote tumor progression towards metastasis. Several studies have now shown the ability of oncogenic RAS to induce IL-8 secretion by tumor cells. For instance, this was demonstrated with various human tumor cell lines modified to overexpress mutated H-RAS, a manipulation that resulted in a substantial upregulation of IL-8 secretion and enhanced tumor vascularization *in vivo* [67]. The same study revealed that ablation of IL-8 function via administration of an anti-IL-8 neutralizing antibody was able to reduce tumor infiltration

with myeloid-derived (CD11b+) cells, including macrophages and granulocytes, while also decreasing tumor vascularization [67]. In another study that utilized a murine model of lung adenocarcinoma with mutant K-RAS, it was also demonstrated that activated K-RAS signaling induces secretion of the murine homologs of IL-8, the cytokines KC and MIP-2. By employing a neutralizing antibody directed against the IL-8 receptor, CXCR2, it was also evident that tumor vascularity directly depended on the activation of the IL-8/IL-8R axis [68]. The findings from these studies supported the idea that oncogenic RAS signaling mediates the secretion of the inflammatory chemokine IL-8, which, acting in a paracrine fashion, can modulate the TME towards a more tumor-promoting and immunosuppressive atmosphere.

Epithelial-mesenchymal transition and inflammation

EMT is a phenotypic switch whereby epithelial cells lose their polarity, extensive cell-to-cell contacts, and expression of characteristic epithelial markers, while acquiring the expression of mesenchymal proteins, increased cell motility, and the ability to invade surrounding tissues [69–71]. Extensively characterized in the context of embryonic development, EMT and its reverse process, called the mesenchymal-epithelial transition (MET) [72, 73], have now been described in the context of cancer [74, 75]. Tumor cells of epithelial origin have been shown to be able to transition into a distinct mesenchymal phenotype, or as more frequently observed, to acquire mesenchymal features while retaining certain epithelial traits [76, 77]. This ‘hybrid’ or ‘intermediate’ tumor phenotype has been validated, for example, in a study with circulating tumor cells (CTCs) from patients with metastatic breast cancer, where CTCs exhibited a defined epithelial or mesenchymal phenotype, but also showed diverse levels of co-expression of epithelial and mesenchymal markers [78]. EMT itself, and the known transcription factors that drive EMT, such as Snail, Slug, Twist, and brachyury, have been linked to both primary tumors and CTCs in regard to advanced tumor stage [79–81], presence of metastases [82], and poor prognosis in numerous cancer types [83–85]. The association of EMT with poor clinical outcome also supports the concept that mesenchymalization (i.e. the acquisition of mesenchymal features) renders cancer cells resistant to the cytotoxic effect of anti-cancer therapeutics, including chemotherapy [86, 87] radiation [88], small-molecule targeted therapies [89, 90] and, as recently demonstrated, lysis by immune effector cells [91, 92].

EMT induces the secretion of inflammatory soluble factors

Although multiple studies have concentrated on understanding the signals that trigger EMT in the context of a tumor, recent reports have begun to investigate how the acquisition of mesenchymal features by carcinoma cells could also contribute to the development of an inflammatory and immunosuppressive TME. In one such study, a comprehensive analysis of the ‘secretory phenotype’ of tumor cells undergoing mesenchymalization via upregulation of brachyury revealed a distinctive set of secreted soluble factors that included, among others, IL-6, IL-8, GRO, GM-CSF, and the angiogenic factors VEGF and angiogenin [93]. The upregulation of IL-8 was particularly interesting in this context, as breast carcinoma cells undergoing brachyury-mediated EMT were shown not only to increase the levels of secreted IL-8 but also to express higher levels of the IL-8 receptors, CXCR1 and CXCR2.

Upregulation of IL-8 secretion by tumor cells undergoing EMT was also demonstrated with human colorectal carcinoma cells growing as colonospheres in culture. In this system, expression of the EMT activator Snail was shown to be responsible for the transcriptional activation of the IL-8 gene via direct binding to E-box motifs found in the IL-8 gene promoter region [94]. Bates and colleagues also examined the role of IL-8 and its receptors in the context of EMT in colorectal carcinomas [95]. Using spheroid models in culture, this study evaluated the induction of EMT via transforming growth factor (TGF)- β in the presence of tumor necrosis factor (TNF)- α derived from activated macrophages [95]. Increased expression of IL-8 and CXCR1 were observed, where functional blockade of CXCR1 was shown to decrease migration of the mesenchymal colon cancer cells.

One of the tumor types commonly associated with the occurrence of a mesenchymal phenotype is triple negative breast cancer (TNBC). Work conducted by Suarez-Carmona and colleagues [39] recently investigated the potential association between EMT and inflammation both *in vitro* and *in vivo* with xenograft models and with patient clinical samples. Similar to other studies, induction of EMT via epidermal growth factor (EGF)-treatment of TNBC lines resulted in a significant enhancement of secreted IL-6, IL-8, and other soluble factors. This result was confirmed with xenografts *in vivo* where mesenchymal tumor cells (vimentin+) had higher levels of IL-6 and IL-8 mRNA than their epithelial (vimentin-) counterparts. A functional assay conducted *in vivo* also demonstrated that conditioned medium derived from EGF-treated (mesenchymal) TNBC cells was able to efficiently recruit immature granulocytic MDSCs, compared to medium derived from epithelial tumor cells. Immunohistochemical analysis of TNBC primary tissues also showed a strong association between the expression of mesenchymal markers and the loss of epithelial E-cadherin with the presence of high numbers of myeloid CD33+ cells, as well as an increased number of blood vessels. Taken together, these findings validate the preclinical observations of the effects of EMT in myeloid cell recruitment and angiogenesis.

Another aspect of tumor EMT that has gained much attention in the oncology field is the role that this phenotypic transition plays in tumor resistance to a range of anti-cancer therapeutics [96]. Acquisition of drug resistance is a common phenomenon observed during tumor progression, including refractoriness to conventional chemotherapy, radiation, and some targeted therapies. In particular, multiple reports have now demonstrated that acquisition of lung cancer resistance to EGFR inhibition is associated, in a subset of patients, with the occurrence of EMT [97–100]. Furthermore, several recent reports have implicated the IL-8/IL-8R axis in the resistance of lung cancer to the widely used EGFR tyrosine kinase inhibitors gefitinib [101] and erlotinib [102]. Observed among various preclinical model systems, lung cancer cells resistant to EGFR inhibition have been shown to transition into a mesenchymal-like phenotype while simultaneously upregulating the expression of both IL-6 and IL-8. Interestingly, blockade of IL-8 signaling was shown to effectively reduce the mesenchymal features of erlotinib-resistant cells, and more importantly, to markedly enhance their susceptibility to erlotinib or to chemotherapies [102]. Work from Liu and colleagues also revealed a central role for the chemokine IL-8 in tumor resistance to the EGFR inhibitor gefitinib [101]. In particular, this study demonstrated that IL-8 levels in the plasma inversely correlated with median progression-free survival of patients with stage IV lung adenocarcinoma with EGFR-mutation positive tumors who also

received gefitinib or erlotinib as their first-line treatment. Collectively, these findings highlight the impact of IL-8 signaling in the generation of resistant phenotypes, and suggest that targeting IL-8 may be a strategy to optimize treatment when EMT-mediated resistance has occurred.

Inflammation triggers and sustains tumor EMT

The ability of multiple stromal-derived soluble factors to induce EMT in tumors has been extensively demonstrated [103]. In particular, the role of TGF- β , EGF, fibroblast growth factor (FGF), insulin-like growth factors, and WNT ligands have been extensively studied in multiple model systems [104–107]. Regarding a potential link between tumor inflammation and EMT, several studies have now begun to investigate whether an inflammatory milieu in the TME could be responsible for the initiation and/or maintenance of a mesenchymalized tumor phenotype (Figure 1). In recent work by Goebel and colleagues, the direct role of CD4⁺ effector T cells on EMT was studied in the context of pancreatic adenocarcinoma and chronic pancreatitis [108]. The authors demonstrated that activated human CD4⁺ CD25⁺ effector T cells induced a spindle-shaped morphology exhibiting reduced E-cadherin expression, high levels of mesenchymal protein expression, and invasive behavior in premalignant ductal epithelial cells or pancreatic adenocarcinoma cells. The effect was prevented via the use of neutralizing antibodies against IL-6 (tocilizumab) or TNF- α (etanercept). Similar observations were made in the context of inflammatory breast cancer (IBC). TNF- α , IL-6, and TGF- β produced by activated human T cells were shown to induce the expression of mesenchymal proteins, including fibronectin, vimentin and ZEB1, in IBC cell lines *in vitro* [109]. These observations are of particular relevance in light of emerging research demonstrating strong immune infiltration in tumors with a more mesenchymal phenotype *in vivo*. A recent report utilized an EMT gene signature to evaluate the occurrence of this phenomenon in various lung cancer datasets, and subsequently analyzed its association with the presence of an ‘inflamed’ TME. This study found that the occurrence of EMT in lung cancer was associated with expression of multiple immune-stimulatory molecules, including CD80, CD86, CD127, OX40L and others, together with overexpression of various immune checkpoint molecules and significantly enhanced infiltration with CD4⁺ Foxp3⁺ regulatory T cells [110].

There is also growing evidence of the role of the chemokine IL-8 in the initiation and maintenance of tumor EMT [111]. Treatment of tumor cells with IL-8 has been shown to induce EMT in colon cancer cells [95], nasopharyngeal carcinoma cells [112] and breast cancer cells [113]. Work conducted in the authors’ laboratory also demonstrated that breast cancer cells, in which EMT was induced via upregulation of the transcription factor brachyury, secrete high levels of IL-8 and simultaneously upregulate the expression of the IL-8 receptors. Blockade of IL-8 signaling was shown to effectively decrease mesenchymal features and invasiveness of the cancer cells, thus demonstrating that a functional IL-8/IL-8R axis is not only essential for the acquisition but also the maintenance of a mesenchymal phenotype. In a study by Visciano and colleagues, the effect of IL-8 on EMT was studied in the context of thyroid cancer [114]. The authors demonstrated that thyroid cancer cells exposed to culture media from mast cells, which are immune cells commonly found at the

invasive areas of thyroid cancer, induced EMT and cell motility via IL-8-mediated activation of a Slug-Akt signaling pathway.

Another interesting connection between EMT and inflammation stems from studies conducted in the context of stress-induced cell senescence. While senescence was initially described as a mechanism that limits cell proliferation in response to oncogenic or DNA damage-induced cellular stress [115], there is evidence that suggests that senescence can also lead to tumor progression through the secretion of a particular set of soluble factors, termed a senescence-associated secretory phenotype (SASP), by the senescent cells [116]. Interestingly, two of the most abundant factors in the SASP are IL-6 and IL-8. Work conducted by Coppe and colleagues demonstrated that conditioned medium derived from fibroblasts induced into a senescent state by exposure to ionizing radiation caused human breast cancer cell lines to undergo cell scattering, acquisition of mesenchymal markers, enhanced invasiveness, and loss of epithelial E-cadherin and cytokeratin expression, consistent with an EMT. Thus, the paracrine activity of the SASP could promote a microenvironment conducive to tumor progression in adjacent tumor cells [117]. Moreover, the authors also analyzed biopsies from human prostate cancer patients obtained before vs. after chemotherapy treatment for the presence of SASP factors. Their analysis demonstrated that tumors contained significantly higher levels of mRNAs encoding for the SASP components IL-6, IL-8, GRO- α , and others following chemotherapy, suggesting that the SASP may occur *in vivo*.

Clinical targeting of IL-8 and IL-6

The influence of the proinflammatory cytokines IL-6 and IL-8 upon tumor initiation and metastasis raises the tantalizing possibility of targeting these molecules as a means of interfering with progression and metastatic dissemination. Therapeutic strategies include using IL-6- or IL-8-specific neutralizing antibodies to starve the tumor microenvironment of these chemokines, or using antibodies or small-molecule inhibitors to target their respective receptors to silence their biological effects. Several IL-6- and IL-8-targeting therapies have been devised, and those that have progressed into clinical development are discussed below.

Siltuximab is a chimeric monoclonal antibody that binds IL-6. In 2014, siltuximab was approved to treat patients with Multicentric Castleman's disease, a lymphoproliferative disorder [118]. This antibody showed promise preclinically for the treatment of multiple myeloma, however it failed to improve progression-free survival or overall survival in a phase II trial in combination with bortezomib [119]. Similarly, evaluation of siltuximab in a phase I/II trial of patients with advanced solid tumors [120], phase II trials in prostate cancer [121, 122], and a phase I/II study in renal cancer [123] showed a favorable safety profile, but this agent generally lacked clinical activity.

Tocilizumab is another IL-6 pathway-targeting humanized monoclonal antibody that acts as an antagonist of IL-6R α and is best known for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis. The first clinical trial testing tocilizumab in cancer was conducted for epithelial ovarian cancer in combination with chemotherapy [124], and demonstrated safety as well as possible immunological benefit, as changes consistent with

reduced suppression of anti-tumor immune responses were reported. Two more clinical trials evaluating tocilizumab in cancer patients are currently ongoing [125, 126].

The only IL-8 neutralizing antibody currently in clinical development is HuMax-IL8 (formerly HuMab10F8). This antibody was previously shown to be well-tolerated and elicited beneficial anti-inflammatory responses in patients with palmoplantar pustulosis, a chronic inflammatory skin disease [127]. A phase 1b dose-escalation, multiple dose trial with HuMax-IL8 is currently ongoing for patients with metastatic or unresectable, locally advanced solid tumors [128]. Another potential approach to minimize the effect of IL-8 consists on the use of small-molecule inhibitors targeting the CXCR1 and CXCR2. Several small molecule antagonists of CXCR2 have been developed and tested for inflammatory lung diseases, but so far none of these agents have been tested in cancer models with the exception of reparixin [129]. Reparixin (formerly known as repertaxin) is a non-competitive allosteric inhibitor of both CXCR1 and CXCR2 that inhibits intracellular signaling without affecting ligand binding [130]. In preclinical investigations reparixin has been shown to reduce tumor growth, reduce metastasis, and deplete CSC populations both alone [131] and in combination with chemotherapy [132]. In clinical studies, it was evaluated for delayed graft dysfunction after kidney transplantation, and was found to improve pancreatic islet survival after transplantation [133]. Reparixin is now being used in a phase I trial in combination with paclitaxel for metastatic triple-negative breast cancer [134].

It is important to point out that the trials discussed above tested cancer patients suffering from more advanced stages of disease. It remains to be seen whether interfering with IL-6 and/or IL-8 signaling earlier in the disease process would lead to a more substantial clinical benefit. Additionally, targeting IL-6 and IL-8 signaling may be more effective in the context of combination with other immunotherapy agents. As mentioned above, disruption of MDSC trafficking using a monoclonal antibody against CXCR2 synergized with PD1 checkpoint blockade in a preclinical model of rhabdomyosarcoma [66]. Investigations of novel combinations of IL-6- and/or IL-8-targeting strategies with other immunotherapy agents may potentially lead to more complete tumor control and should be an area of high priority research in the future.

Concluding remarks

As our understanding of the role of inflammation in cancer continues to improve, new opportunities arise for therapeutic interventions against tumor progression based on the modulation of inflammation at the tumor site. One central mechanism that links inflammation to cancer progression is the phenomenon of EMT, which contributes not only to the acquisition of a more metastatic tumor phenotype, but also to the secretion of a range of inflammatory cytokines, including IL-6 and IL-8. These cytokines subsequently promote the recruitment and polarization of immune cells towards a pro-tumor environment to aid in the maintenance of malignancy, providing potential therapeutic targets in the clinic. We hypothesize that therapeutic strategies aimed at starving the tumor microenvironment from these inflammatory mediators could interfere with tumor progression and metastatic dissemination by reverting and/or preventing the occurrence of EMT.

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Figure 1. Inflammation and EMT at the primary tumor site

Pro-inflammatory soluble factors secreted by cancer cells, including IL-6 and IL-8, promote the recruitment of various immune cell populations to the site of a primary tumor. Cancer cell signaling adaptations, notably through oncogenic signaling involving Ras, EGFR and others, are known drivers of tumor secretion of pro-inflammatory mediators. In addition, soluble factors secreted by cancer cells or the surrounding stroma undergoing senescence (SASP), can also contribute to the inflammatory milieu of an established tumor. One of the consequences of tumor-driven inflammation is the induction of tumor phenotypic changes, termed epithelial-mesenchymal transition (EMT), which endow epithelial cells with mesenchymal features, including high motility, invasiveness and the ability to disseminate and metastasize. These ‘mesenchymalized’ tumor cells are also prone to secrete high levels of IL-6, IL-8 and other factors that could further contribute to tumor inflammation.