Targeting Myelomonocytic Cells to Revert Inflammation-Dependent Cancer Promotion

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Abstract

Tumor development and progression are strongly linked to inflammation and the presence of tumor-associated macrophages (TAMs). In murine tumors, antitumor activity can be achieved by targeting TAM recruitment, survival, activation, polarization, effector signaling, or extracellular matrix interactions. Thus, it may be possible to increase the efficacy of conventional cancer therapeutic strategies by targeting TAMs. (Cancer Res 2005; 65(20): 9113-6)

Introduction

As early as the 19th century, it was perceived that cancer is linked to inflammation (1). Although this perception waned over time, recent years have seen a renaissance of the inflammation-cancer connection stemming from different lines of work leading to a generally accepted paradigm (1–3). Epidemiologic studies have revealed that chronic inflammation predisposes to different forms of cancer, such as colon, prostate, and liver cancer, and that usage of nonsteroidal antiinflammatory agents can protect against the emergence of various tumors. An inflammatory component is present in the microenvironment of most neoplastic tissues, including those not causally related to an obvious inflammatory process. Hallmarks of cancer-associated inflammation include the infiltration of WBC, the presence of polypeptide messengers of inflammation (cytokines and chemokines), and the occurrence of tissue remodeling and angiogenesis.

Strong evidence suggests that cancer-associated inflammation promotes tumor growth and progression (1–3). By the late 1970s, it was found that tumor growth is promoted by tumor-associated macrophages (TAMs), a major leukocyte population present in tumors (1–4). Accordingly, in many but not all human tumors, a high frequency of infiltrating TAMs is associated with poor prognosis. Interestingly, this pathologic finding has re-emerged in the postgenomic era: genes associated with leukocyte or macrophage infiltration (e.g., CD68) are part of the molecular signatures which herald poor prognosis in lymphomas and breast carcinomas (5). Gene-modified mice and cell transfer have provided direct evidence for the pro-tumor function of myeloid cells and their effector molecules. These results raise the interesting possibility of targeting myelomonocytic cells associated with cancer as an innovative therapeutic strategy. Here, we will concisely review the current status and potential of anti-TAM strategies in cancer therapy (Fig. 1).

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Targeting recruitment and survival

TAMs derived from circulating monocytes and circulating monocyctic precursors are attracted into tumors in response to chemokines (e.g., CCL2 and CCL5) and cytokines [vascular endothelial growth factor (VEGF), platelet-derived growth factor, and macrophage colony-stimulating factor (M-CSF)]. Cell and gene transfer as well as gene-modified mice have provided the proof of concept that inhibiting monocyte recruitment by blocking attractant and survival factors (e.g., CCL2 or M-CSF) can result in an inhibition of growth in tumors, including breast carcinoma, sarcoma, and melanoma. However, in agreement with the “macrophage balance” hypothesis (4), flooding tumors with macrophages can result in growth retardation. Chemokines are primarily chemotactic molecules, with the additional capacity to activate a distinct transcriptional program that amplifies inflammation and matrix remodeling (see references in refs. 1–3). Tumor cells themselves also express receptors for chemokines that regulate proliferation, survival, invasion, and metastasis. In particular, CXCR4 is widely expressed or overexpressed in various human solid tumors, including ovarian carcinoma, pancreatic carcinoma, papillary thyroid carcinoma, and breast carcinoma. Thus, targeting selected chemokine receptors has the potential to influence the growth and metastasis of selected human tumors at the level of stromal TAMs as well as on cancer cells themselves.

Recent results have shed new light on the links between chemokines and the genetic events that cause cancer. The CXCR4 receptor lies downstream of the von Hippel/Lindau/hypoxia-inducible factor axis. Transfer of activated ras into a cervical carcinoma line, HeLa, induces IL-8/CXCL8 production that is sufficient to promote angiogenesis and progression. Finally, a frequent early and sufficient gene rearrangement that causes papillary thyroid carcinoma activates an inflammatory genetic program that includes CXCR4 and inflammatory chemokines in primary human thyrocytes. The emerging direct connections between oncogenes, inflammatory mediators, and the chemokine system provide an impetus for exploring the anticancer potential of antiinflammatory strategies.

VEGF and M-CSF (or CSF1) are cytokines commonly produced by tumors that interact with tyrosine kinase receptors and elicit monocyte migration. There is evidence that M-CSF and VEGF can significantly contribute to macrophage recruitment in tumors. These molecules also promote macrophage survival and proliferation, the latter generally limited to murine TAMs. Studies in M-CSF-deficient mice (op/op) provide strong support to the concept of the pro-tumor function of the mononuclear phagocyte system (see ref. 6 for complete references). It was originally reported that M-CSF deficiency in op/op mice diminished macrophage recruitment, stroma formation, and tumor growth in the Lewis lung carcinoma model. However, in a mammary carcinoma model, M-CSF deficiency did not affect the early stages of tumor development, but instead reduced progression to later
stages of invasive carcinoma and metastasis. Genetic replacement of M-CSF production restored macrophage infiltration as well as malignant behavior in this system.

VEGF is a potent angiogenic factor as well as a monocyte attractant that contributes to TAM recruitment. TAM promotes angiogenesis and there is evidence that inhibition of TAM recruitment plays an important role in antiangiogenic strategies (7).

A variety of other agents can also target macrophages in vivo. Macrophage toxins such as silica have provided early evidence for the pro-tumor function of TAM. Bisphosphonates are in clinical use to protect bones against cancer-associated hypercalcemia. These compounds also inhibit bone metastasis and tumor neoangiogenesis in vivo by impairing VEGF signaling and matrix metalloproteinase-9 expression by stromal macrophages (8). The halogenated bisphosphonate derivative clodronate is a macrophage toxin which depletes selected macrophage populations. Given the current clinical usage of this and similar agents, it will be important to assess whether they have potential as TAM toxins. Yondelis (Trabectedin) is a recently developed antitumor agent that inhibits NF-Y, a transcription factor of major importance for mononuclear phagocyte differentiation. It was recently observed that this agent has a unique preferential toxicity for macrophages, including TAMs, and that it inhibits selected TAM functions (9). The actual contribution of TAM targeting to therapeutic agents such as Bevacizumab or Yondelis (9) and the potential of more targeted strategies remains to be elucidated.

Genetic manipulations that allow selective depletion of macrophages or that cause myeloid lineage-specific gene inactivation offer new tools to dissect the role of myeloid cells and their products in tumor progression. For instance, a transgenic mouse line has been developed that expresses a Fas-based suicide gene under the macrophage-specific c-fms promoter. A drug inducing the dimerization of the suicide protein, activates the Fas-mediated apoptosis depleting 70% to 95% of the transgene-expressing population (10). Identification of promoters specific for restricted subpopulations will foster this line of research.

Targeting activation and polarization

Florid inflammation can promote or predispose to cancer. Systemic or myeloid-specific inactivation of nuclear factor κB (NF-κB) can protect against tumor development in the colon and liver (11, 12). However, TAMs isolated from a variety of established progressing tumors, where they are part of a long-term "smoldering" inflammatory reaction, have defective activation in the NF-κB pathway in response to TLR agonists as well because there is also evidence for a protective function of NF-κB, a duality of role reminiscent of the macrophage balance.
TAM from murine and human tumors investigated to date have an IL-10^high^ IL-12^low^, TNF^low^, IL-1^low^, scavenger, and mannose receptor^high^ phenotype. This phenotype is characteristic of so-called M2 macrophages that are oriented to taming and regulating adaptive immunity, tissue remodeling, and growth promotion. IL-10 contributes to the TAM M2 phenotype. Consistent with these in vitro properties, a combination of CpG oligonucleotides and anti-IL-10R is sufficient to convert TAM phenotype from M2 to M1, the latter of which is oriented to promote both innate and adaptive immunity. As an illustration of the potential antitumor utility of this combination, established carcinomas can be regressed in vivo by intratumoral injection of TAM-activating chemokines such as CCL16/LEC (13) or CCL20/MIP3a, followed by treatment with CpG oligonucleotides and anti-IL-10R.

Targeting effector molecules

Cyclooxygenase (COX) is a key enzyme in the prostanooid biosynthetic pathway. COX-2 is up-regulated by activated oncogenes (i.e., β-catenin, MET) but is also produced by TAMs in response to tumor-derived factors like mucin in the case of colon cancer. The usage of COX-2 inhibitors in the form of nonsteroidal antiinflammatory drugs is associated with reduced risk of diverse tumors (colorectal, esophagus, lung, stomach, and ovary). Selective COX-2 inhibitors are now thought as part of combination therapy. Immature myeloid cells expanded in pathologic conditions, such as in acute or chronic infections or in tumors, can suppress T lymphocytes through an unbalanced iNOS and Arg-1 activity. Selective inhibitors of these enzymes or molecules interfering with reactive oxygen species generation have proven beneficial in controlling myeloid suppression in vitro but are often toxic in vivo. Interestingly, coupling a NO-releasing moiety to aspirin has been shown to provide feedback inhibition of iNOS activity, suppression of oxygen species, and peroxynitrite generation, thereby correcting myeloid cell suppression in vivo (14). Species-related differences should be considered in targeting arginase. Arginase is induced by IL-4 and IL-13 in murine macrophages and has been considered to be strongly associated with at least one form of M2 macrophage (M2a). However, we and others have failed to observe induction of arginase in M2-polarized human monocytes and macrophages.

Indoleamine 2,3-dioxygenase (IDO) is the rate-limiting enzyme in tryptophan catabolism. Tryptophan starvation by IDO consumption is the first line of protection against microbial invaders and intracellular parasites, but it also inhibits T cell activation, whereas products of tryptophan catabolism, such as kynurenic derivatives and oxygen free radicals, limit T cell proliferation and survival. Mononuclear cells that invade experimental tumors and tumor-draining nodes have been shown to express high levels of IDO activity, thus constituting a powerful inducer of local immune suppression (15). Whatever is produced by tumor or infiltrating mononuclear cells, IDO can be inhibited to increase the efficacy of cancer chemotherapeutic agents (16) and/or immunotherapy (17).

References


Targeting the interaction with the extracellular matrix

Cell-produced extracellular matrix modulates communication and interaction of embedded cells to create either a stable or dynamic environment. Macrophages produce and bind matricellular proteins. Macrophage-extracellular matrix interactions are bidirectional and produce a variety of effects involving inflammation, tissue remodeling, and repair, which in a tumor context lead to progression and metastasis or, in certain conditions, regression. Among the matricellular proteins, the secreted protein acidic and rich in cysteine (SPARC) has gained much interest in cancer, being either up-regulated or down-regulated in progressing tumors. This finding has been confirmed by several recent gene expression profiles testing a variety of tumors and, in some cases, their response to therapies. The often-contrasting results stem from the careless determination of the cellular source of SPARC in the system under investigation. SPARC produced by macrophages present in tumor stroma can dominate tumor-produced SPARC in directing collagen density, leukocyte, and blood vessel infiltration (19). This feature offers the possibility of intervening to shut down SPARC expression in macrophages. Recently, unidentified matricellular components have been suggested to elicit the antibody response that kindles the innate, inflammatory response which drives transformation in a transgenic skin human papillomavirus model (20). Although B cells, which do not infiltrate the tumor, operate like a “remote control” (21), TAM-digested extracellular matrix might provide the antigen for antibody recognition as well as an array of matrix-derived endogenous promoters and inhibitors of angiogenesis (22). Subsequently, proteases could then modify the bioavailability of cytokines, chemokines, and receptors as feedback to the many mechanisms described above.

Concluding Remarks

Targeting cancer-promoting inflammatory reactions in a preventative or therapeutic setting is at an early stage. TAMs are key components of cancer-associated inflammation. Several lines of evidence, including genetic manipulations, suggest that recruitment and survival of TAM, transcription factors that control TAM activation and polarization, and TAM effector molecules can represent valuable targets for developing innovative therapeutic strategies, complementary to established approaches.

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