Role of Chemokines and Chemokine Receptors in Shaping the Effector Phase of the Antitumor Immune Response

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Abstract

Immune system–mediated eradication of neoplastic cells requires induction of a strong long-lasting antitumor T-cell response. However, generation of tumor-specific effector T cells does not necessarily result in tumor clearance. CTL must first be able to migrate to the tumor site, infiltrate the tumor tissue, and interact with the target to finally trigger effector functions indispensable for tumor destruction. Chemokines are involved in circulation, homing, retention, and activation of immunocompetent cells. Although some of them are known to contribute to tumor growth and metastasis, others are responsible for changes in the tumor microenvironment that lead to extensive infiltration of lymphocytes, resulting in tumor eradication. Given their chemotaxic and activating properties, a role for chemokines in the development of the effector phase of the antitumor immune response has been suggested. Here, we emphasize the role of the chemokine–chemokine receptor network at multiple levels of the T-cell–mediated antitumor immune response. The identification of chemokine-dependent molecular mechanisms implicated in tumor-specific CTL trafficking, retention, and regulation of their in situ effector functions may offer new perspectives for development of innovative immunotherapeutic approaches to cancer treatment. *Cancer Res*; 72(24); 6325–32. ©2012 AACR.

Introduction

The identification of tumor-associated antigens (TAA) and the isolation of tumor-specific cytotoxic T cells have led to great efforts in developing immunotherapeutic approaches to overcoming tumor invasion. Immunotherapy represents a promising approach to cancer treatment, with less severe side effects than conventional strategies. Major strategies have focused on the induction of T-cell–mediated antitumor responses. However, the generation of antigen-specific tumor-reactive T cells has rarely been translated into therapeutic success. One of the reasons for the failure of the immune system to eradicate cancer cells is a defect in T-cell migration to the tumor site (1). To destroy established tumors, CTL must traffic to and infiltrate the tumor tissue before specific activation and triggering of target cell death. The dissection of cellular and molecular processes that enhance T-cell recruitment and ultimately lead to tumor elimination is therefore a critical step in optimization of current cancer immunotherapy protocols.

Chemokines coordinate circulation, homing, and retention of immune cells. Originally characterized for their ability to induce leukocyte chemoattraction, they are now recognized to orchestrate a wide array of leukocyte functions during inflammation and immunity (2). Indeed, in addition to their chemotactic properties, chemokines can directly regulate T-cell development, priming, and effector functions (3). In the context of cancer immunosurveillance, chemokines orchestrate the spatiotemporal distribution of immunocompetent cells crucial for induction of antitumor immune response and optimal effector function (4, 5). Chemokines constitute a large family of small, mostly secreted proteins comprising more than 50 members, which interact with 20 chemokine receptors. Chemokine receptors are G-protein–coupled 7-transmembrane–domain receptors responsible not only for triggering intracellular signals resulting in cell polarization, migration, and adhesion, but also for contributing to gene expression, cell proliferation, and survival (2). Most chemokines bind to more than 1 receptor. On the other hand, chemokine receptors display overlapping ligand specificities with variable affinity and functional activities (3).

There is now overwhelming evidence that the chemokine–chemokine receptor system is directly or indirectly involved in tumor development (6). On the basis of their role in cell migration, chemokines contribute to tumor dissemination and metastasis. Moreover, chemokine-triggered signaling pathways can facilitate tumor cell proliferation and contribute to neovascularization. Tumor-derived chemokines are also

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doi: 10.1158/0008-5472.CAN-12-2027
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responsible for shaping the tumor microenvironment into an immunosuppressive site, determining the qualitative and quantitative composition of tumor-infiltrating immune cells and affecting their maturation and activation status (7). In consequence, tumors seem to use chemokines to evade immunosurveillance and actively progress. Nevertheless, expression of some chemokines within the tumor bed has been associated with an effective antitumor immune response, an angiostatic effect, a low recurrence rate and increased patient survival. Indeed, some chemokines are responsible for changes in chemoattractive properties of the tumor microenvironment that allow extensive infiltration of leukocytes (7). Thus, chemokines and chemokine receptors represent valuable targets for optimizing antitumor immune responses. In this context, the major concern of tumor immunologists is to better understand chemokine-mediated pathways involved in T-cell recruitment at the tumor site and in regulating their intratumoral effector functions. In this review, we present findings implicating chemokines in regulation of the CTL-mediated effector phase of the antitumor immune response and we provide insights into their therapeutic applications.

**Role of Chemokines in Priming the T-Cell–Mediated Immune Response**

Development of an effective antitumor immune response relies on the coordinated interactions of immunocompetent cells, the spatiotemporal distribution of which is in part orchestrated by chemokines (Fig. 1). Acting through their cognate receptors, chemokines regulate trafficking between the tumor site and lymph nodes. To become competent killer cells, CTL require efficient priming by professional antigen-presenting cells (APC) and cognate licensing of dendritic cells by CD4+ T cells (8). For this purpose, naïve CD8+ T cells continuously traffic through secondary lymphoid organs in which they systematically scan the surface of dendritic cells searching for TAA. Naïve T cells express CCR7, which recognizes constitutively expressed CCL19 and CCL21. CCL21, produced by lymph nodes, Peyer's patch–associated high endothelial venules, and afferent lymphatic vessels, triggers a multistep process for recruitment of naïve lymphocytes (9). Similarly, CCL21–CCR7 signaling is involved in trafficking of antigen-presenting dendritic cells. Indeed, their maturation into potent APC implies downregulation of tissue-specific chemokine receptors, such as CCR1, CCR5, and CCR6, and upregulation of CCR7, which guides dendritic cells from sites of antigen exposure to the local lymph nodes via draining afferent lymphatic vessels (10). The pivotal role of CCR7 in these processes was shown in CCR7–deficient mice, which displayed reduced numbers of naïve T cells in secondary lymphoid organs (11). Once in the lymph nodes, T cells display high basal motility, enabling them to scan up to several thousand APC per hour. These steady-state movements are dependent on Gαs–coupled chemokine receptor signaling triggered by CCL19 and CCL21 present in the lymph node T-cell zone (12).

The major biologic relevance of naïve T-cell motility within lymph nodes is to ensure recognition of a few antigen-bearing dendritic cells by rare specific T cells. However, random migration of T cells does not seem to be efficient enough to provide CD4 T-cell help for CD8 T-cell priming, where 2 lymphocyte types have to encounter the same APC (13). It has been shown that CCL19 secreted by mature dendritic cells increases naïve CD4 T-cell scanning behavior and their response to rare cognate antigens (14). Moreover, engagement of naïve CD4 T cells with APC triggers secretion of CCL3 and CCL4, which favor CCR5-dependent guidance of naïve CD8 T cells toward dendritic cells (DC)-CD4 T-cell conjugates (15). Interestingly, CCR5–dependent recruitment of CD8 T cells to dendritic cells engaging TAA-specific T cells increases the efficiency of alternative TAA–specific naïve CD8 T-cell priming (16).

Following the antigen encounter and T-cell expansion, a modification in the general chemokine receptor expression profile is required to enable appropriate redistribution of activated T cells. This modification consists of downregulation of receptors that mediate entry and the encounter with APC in the lymph node, and of upregulation of other receptors to first egress from the lymph node and then sensitize T cells to infiltrate the tumor site. Pertussis toxin has been shown to affect lymphocyte egress from the lymph node, suggesting an implication of chemokine receptors. Indeed, one of the initial events in effector T-cell differentiation is downregulation of CCR7 and upregulation of receptors specific to chemokines expressed in target tissues, such as CCR1, CCR2, CCR3, CCR5, and CXCR3 (17). Acquisition of an appropriate migration program is thus crucial for targeting the right cell to the right place.

**Regulation of T-Cell Recruitment at the Tumor Site by Chemokines**

To exert their functions, recently primed T cells leave the lymph node and migrate to the tumor site, in which they physically engage cognate T-cell receptor (TCR) ligand-expressing targets. Chemokines play a major role in the recruitment of effector T cells within the tumor microenvironment. Antitumor CTL respond to numerous inflammatory chemokines, mainly CCL3 (18), CCL5 (19), CCL20 (20), and CXCL10 (21), which can be produced at the tumor site (22). Therefore, the intratumoral production of chemokines, which determine optimal T-cell recruitment, is one of the key factors in an efficient antitumor immune response. In this context, CCL5 was one of the first chemokines implicated in regulating antitumor immunity (19). A role for CCR5 in T-cell recruitment to the tumor site has been documented and local production of CCL5 or CCL3 induces selective recruitment of CD8 T cells and CTL-dependent tumor suppression in mouse models (23). CCR5 ligands are detected in many human tumors, including non–small-cell lung carcinoma (NSCLC), and can induce T-cell infiltration. However, the role of CCL5 in the antitumor immune response remains controversial. In NSCLC, the production of CCL5 has been associated with an active lymphocyte–mediated response and represents a positive predictive factor for patient survival (24). In contrast, high levels of CCL5 have been reported to correlate with poor prognosis in breast and cervical carcinomas (25). Although the cellular infiltrates were not investigated in these studies, it is conceivable that disease progression was related to tumor escape mechanisms.
Chemokines and the Antitumor Immune Response

Figure 1. Chemokine network in the antitumor immune response. Malignant cells express pathogen-associated molecular patterns (PAMP) that can be recognized by pattern recognition receptors (PRR) on dendritic cells (DC) and macrophages (M/M), triggering release of chemokines. This results in recruitment and activation of M/M, NK, and NKT cells, which are able to lyse tumor cells. DC phagocytose apoptotic tumor cells and HSP-complexed tumor-derived peptides. Upon maturation, DC change their homing proprieties by downregulating tissue-specific chemokine receptors and upregulating CCR7 that guides them to CCL19/CCL21-rich lymph nodes (LN), where they present processed tumor peptides to CD4⁺ and CD8⁺ T cells. Activated T cells upregulate expression of chemokine receptors including CCR5s and CXCR3s, and in response to intratumoral chemokines, circulating CTL infiltrate the tumor to destroy malignant cells. Tumor-derived chemokines are also responsible for recruitment of Treg cells and MDSC, which participate in establishment of a protumoral microenvironment. Ag, antigen; IDC, immature DC.
through concurrent recruitment of immunosuppressive cell populations, such as tumor-associated macrophages and regulatory T (Treg) cells, or triggering of tumor-infiltrating lymphocyte (TIL) apoptosis (26). Conversely, other groups provided evidence for CCL3 and CCL5-induced T-cell proliferation and activation (27, 28).

Among other chemokines implicated in tumor infiltration by immune cells, CX3CL1 and CXCL16 have been associated with high numbers of CD8+ and CD4+ TIL and with good prognosis in colorectal cancer (29). CCL20 has been detected in breast cancer, in which it may be responsible for recruitment of CCR6+ memory T-cell subsets (30). The main chemokines attracting effector cells seem to be the CXCR3 ligands CXCL9 and CXCL10. In addition to their angiostatic activity, these chemokines participate in the antitumor immune response through recruitment of T and natural killer (NK) cells (23). In renal cell carcinoma, intratumoral expression of CXCL9 and CXCL10 coincided with a high degree of CD8 T-cell infiltration and elicited an inverse correlation with tumor growth and recurrence after curative surgery (31). High levels of CXCL9 have also been associated with strong infiltration of malignant melanoma by CD8 T cells and improvement in patient survival (32). Thus, it seems evident that chemokines contribute to the establishment of the immune response by orchestrating the distribution of its key cellular components and delivering the generated effectors to the tumor site. Whether intratumoral chemokines promote immune surveillance or tumor escape depends on the composition of cell infiltrates, which shape the environmental context through an immunoediting process.

Intratumoral T-Cell Location, Motility, and Retention

Positioning of CTL within tumor tissues is critical for an efficient antitumor immune response. After extravasation, CTL must migrate through the interstitial space of the tumor to recognize and kill target cells. Thus far, little is known about the intratumoral migration of infiltrating CTL. In experimental studies, CD8 T cells were mostly observed at the tumor periphery, with limited infiltration into the tumor mass. A similar pattern was identified in human tissue sections from metastatic melanoma. In NSCLC, T cells accumulate in stromal regions in which chemokines likely participate in controlling their motility and their entry into tumor islets (33).

Before establishing stable contact with target cells, TIL migrate randomly within the tumor microenvironment, arguing against the early concept of T-cell guidance by a long-range chemokine gradient. Two-photon microscopy studies provided insight into the dynamics of infiltration and elimination of solid tumors by immune cells (34, 35). After diapedesis, effector T cells initially display random migration and start engaging a transient antigen-independent interaction with target cells. CTL that encounter antigen-expressing tumor cells, arrest their migration to establish a stable contact with the target. This leads to release of cytokines and cytotoxic granules resulting in tumor cell death. Once cancer cells are cleared, CTL resume motility to further search for new target cells. Interestingly, nonspecific tumor T cells can deeply infiltrate tumor tissues only upon tumor destruction by antigen-specific CTL (35). This suggests that changes in the tumor microenvironment, such as secretion of chemokines induced by destruction in tumor architecture, determine deep lymphocyte infiltration. Therefore, delivery of appropriate chemokines into the tumor, reminiscent of what takes place during an effective T-cell response, would induce extensive infiltration of effector cells, and thereby tumor destruction.

The contribution of chemokine receptors in T-cell retention at the tumor site is not well documented. We recently reported that recruitment of CCR5 at the immune synapse formed between TIL and tumor cells, resulted in inhibition of T-cell responsiveness to CCL5 chemokine stimulation (36). An alternative mechanism of CTL retention in epithelial tumors could implicate CCR6. CCR6+ T cells were found to be more frequent in CD8 subpopulations isolated from TIL than from PBL (36). This observation, together with efficient homing of CCR6+ CTL to the tumor site, suggests that CCR6 is not involved in T-cell recruitment to NSCLC but may play a local role. Apart from its function in cell trafficking, CCR6 was reported to be crucial for cell activation and conformational changes in integrins (37). Furthermore, it has been shown that the interaction of CCR6 with its unique ligand, CCL20, is a critical event in the arrest of effector/memory T cells on endothelial cells (38). It is therefore conceivable that intratumoral induction of CCR6, together with CD103, play a role in T-cell retention at the tumor site.

Costimulatory Role of Chemokines–Chemokine Receptors in T-Cell Activation

Although there is a considerable evidence implicating chemokines in antigen-experienced T-cell recruitment to the tumor site, their role in T-cell effector function is begging for intensified investigation. It has been widely reported that engagement of chemokine receptors triggers a "go" signal that competes with TCR-mediated "stop" signals, and thus negatively influences the stability and duration of the immune synapse (39). Indeed, the gradient of some chemokines, including CXCL10 and CCL19 or CCL21, renders T cells ignorant of antigen-peptide-MHC (pMHC), thus suppressing their activation. However, CCL19 secreted by antigen-activated dendritic cells induces T-cell polarization and motility, resulting in improved scanning of APC, thus increasing cognate pMHC encounters (14).

Chemokines such as CXCL12 were also reported to enhance adhesion of T cells to dendritic cells by regulating the avidity/affinity of key integrins, including leukocyte function-associated antigen (LFA)-1 (37). Other chemokines, namely CCR7 ligands bound on dendritic cells surface, may promote T-cell activation by improving immune synapse formation (40). CCR5 and CXCR4 can be recruited to the immune synapse during T-cell stimulation by APC, leading to a reduction in T-cell sensitivity to other chemokine sources and enhanced T-cell responses (27). It has also been proposed that APC-derived chemokines can act as costimulatory molecules for engaged T
Table 1. Experimental and clinical trials based on intratumoral delivery of human chemokines

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NOTE: Respective human chemokines, DC, or adenoviral vectors encoding human chemokines were injected directly at the tumor site.

Abbreviations: Ad, adenovirus; DC, dendritic cells; (H), human; (M), mouse; r: recombinant.
cells through chemokine receptors relocalized at the immune synapse (27).

Role of Chemokines in Shaping the Tumor Microenvironment

The tumor microenvironment is characterized by chronic inflammation with the presence of cytokines and chemokines, the profile of which dictates neoplastic outcome (7). Indeed, chemokines mediate accumulation of immunocompetent cells and participate in shaping a tumor-promoting or -suppressive microenvironment. CCR5 and CXCR3 predominate on Th1 cells, whereas Th2 cells preferentially express CCR3, CCR4, and CCR8. At the tumor site, Th1 cells colocalize with macrophages and neutrophils, enhancing the cell-mediated immune response. In contrast, Th2-type inflammation is considered to be protumoral and is associated with a poor prognosis (41).

Chemokine receptor patterns that guide CD8 T cells to target tissues have not been studied as extensively as CD4 T cells but seem to be similar. Upon antigen-reencounter, CD8 T cells secrete inflammatory chemokines, such as CCL3 and CCL5, which increase infiltration of neutrophils, monocytes, and Th1 lymphocytes, and thus contribute to so-called auto-recruitment of CTL, resulting in amplification of effector responses. However, the protective activity of TIL is often compromised by immunosuppressive tumor microenvironment components, including Treg cells. Treg can be actively attracted to the tumor mostly via CCR4. Infiltration by Treg of ovarian tumors producing high levels of CCL17 and CCL22 correlated with unfavorable prognosis (42). Treg cells, recruited through CCL22-CCR4, can be activated in lymphoid infiltrates surrounding breast tumors, leading to an adverse clinical outcome (43). Other immunosuppressive cells participating in shaping the tumor microenvironment are myeloid-derived suppressor cells (MDSC; Fig. 1). Once recruited within tumors in a CCR2, CXCR4, or CXCR2-dependent manner, MDSC have a significant effect on tumor progression, mainly through suppression of antitumor effectors (44). Thus, by determining the composition of cellular infiltrates, intratumoral chemokines continuously shape the tumor microenvironment and regulate the extent of antitumor immune responses.

Chemokines in Cancer Immunotherapy

Strategies of chemokine–chemokine receptor–based tumor immunotherapy are aimed at eradicating tumors by inhibiting survival and metastasis of malignant cells. The overexpression of chemokines at the tumor site usually resulted in infiltration by host leukocytes; however, disease outcome was more divergent and related to the nature of the injected chemokines, the subset of recruited immune cells and the tumor model (Table 1). In mice, intratumoral delivery of chemokines can induce tumor suppression and immunity to subsequent tumor challenge through recruitment of dendritic cells, NK, and T cells (5). However, the efficacy of such approaches seems limited in humans (29). As chemokines are also responsible for attraction of immunosuppressive cells, such as Treg cells, blocking the activity of the host CCR5 has been proposed for improving the potency of dendritic cell–based vaccines against melanoma (45). Combination of chemokines with cytokines for cancer immunotherapy seems to deserve consideration. A combination of XCL1 and interleukin (IL)-2 has been reported to provide enhanced and long-term antitumor immunity (46).

Other approaches to chemokine-based tumor immunotherapy include vaccination strategies with TAA. Despite a great deal of effort, the rate of objective cancer regression in vaccinated patients has remained weak. Among the limitations of such vaccines are the insufficient numbers of recruited effector cells and their inappropriate activation in an immunosuppressive tumor microenvironment (1). In this context, manipulating the chemokine network may represent an attractive adjuvant strategy (Table 1). A vaccine based on XCL1- and IL-2–secreting neuroblastoma cells induced an increase in T-cell infiltration and resulted in complete or partial tumor remission in vaccinated patients (47). Adoptive immunotherapy is currently one of the most promising approaches, with significant positive results in preclinical and clinical trials (48, 49). The success of adoptive therapy depends on the optimal selection and/or genetic engineering of antigen-specific cells, induction of their proliferation while preserving effector functions, engraftment ability, and efficient homing to the tumor (50, 51). Because recruitment of transfused lymphocytes at the tumor site is one of the critical steps, intratumoral expression of adequate chemokines represents one of the strategies for improving adoptive immunotherapy. Moreover, redirecting the migratory properties of adoptively transferred T cells toward chemokine-secreting tumors can be achieved by genetic expression of appropriate chemokine receptors. Thus, the intratumoral production of chemokines, which determine the optimal CTL recruitment, is one of the key factors for efficient antitumor responses. Any alteration can result in tumor evasion and represent one of the conceivable reasons for the failure of adoptive transfer or vaccination-based immunotherapies (4).

Concluding Remarks

The success of cancer immunotherapeutic strategies relies on the generation of efficacious effector mechanisms associated with the presence of high-avidity tumor-specific CTL. Chemokines contribute to induction of an effective immune response, orchestrating distribution of its key cellular components, and delivering the generated effectors to the target. It should, however, be noted that the chemokine–chemokine receptor network is also implicated in immune system homeostasis, thus limiting its manipulation in a clinical setting. Despite these obstacles, intensified investigation of the role of chemokines in tumor immunosurveillance and immunosuppression may provide a gateway to development of innovative and effective strategies for cancer immunotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: K. Franciszkiewicz, M. Routet, C. Combadère, F. Mami-Chouaib
Development of methodology: F. Mami-Chouaib

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