

Open Access

Cytokines, Chemokines, and "Marshalling for War"

Gloria J Morris*

Department of Medicine, Division of Hematology/Oncology, The Tisch Cancer Institute, The Mount Sinai Hospital, The Mount Sinai School of Medicine, New York, NY, USA

Chemokines are peptides that are secreted by epithelial cells, stromal endothelial cells and fibroblasts, and leukocytes, which attract and actively recruit leukocytes to areas of inflammation. They are recruited to fight infection as a host response to foreign organisms, and also have been shown to play a role not only in host response to tumor and cancer-related inflammation, but also a role in promoting cancer metastases and invasion [1,2].

In this Special Issue of the Journal of Cell Science and Therapy, four articles on cytokine research are highlighted, and their impacts on the response(s) of the immune system are contextualized. Two reports discuss stimulating the immune system to either fight disease or protect the host against the effects of disease treatment. Specifically, Nicolete and Nicolete [3] report new technology employing a biodegradable micro particulate system stimulating the release of leukotriene LTB4 to the lungs, thus enhancing a strategy to boost host defense against specific airway infection from fungal histoplasmosis. Logani et al. [4] review the effects of millimeter wave therapy (MMWT) utilized in Russia and Eastern Europe as treatment of disease, and propose its use as a complementary therapeutic modality to boost the immune system when chemotherapy and/or radiotherapy is used to treat cancer. Based on experimental studies where MMWT has been shown to reduce the spread of melanoma [5]; the authors discuss their findings that MMWT can enhance T-cell mediated immunity, and accelerate recovery of NK cell activity in mice treated with chemotherapy, as associated with the restoration of spontaneous release of TNF-a by peritoneal macrophages.

Two other reports discuss the impact of cytokines on disease-specific inflammation. Scholten et al. [6] show that acute liver injury is combated by the recruitment of immune cells and neutrophils by the induction of chemokines in the leukocyte chemoattractant receptor network (CXC family) and ligands such as CXCL9 and CXCL1; their infiltration into liver tissue is associated with the fibrosis seen pathologically in many chronic liver diseases including viral hepatidites, steatohepatidites, or autoimmune disorders. In their study, mice treated with rCXCL9 had increased CXCL1 concentration in hepatic cells, and increased infiltration of neutrophils. Conversely, Aoyagi and Matsui [7] highlight cytokine signaling as a key event in the inflammatory response after cardiac injury: the interaction between leukocytes, cardiac fibroblasts, and cardiomyocytes may instead be detrimental and lead to further heart failure. They also note that activation of mammalian target of rapamycin (mTOR) in cardiomyocytes suppresses inflammatory reaction in pathologic cardiac hypertrophy, with an associated decrease in IL-6 and IL-1 production and less accumulation or recruitment of macrophages, thus better preserving cardiac function by preventing damage during remodeling.

Can these above studies be distilled to hypothesize the benefit of harnessing cytokines in host defense and even offense as in clinical therapeutics? Can these cytokine pathways be specifically targeted to enhance treatment, harnessed as adjuncts to cancer therapy, and even a graft-versus-host response against tumor? Are they able to be specifically targeted to inhibit cancer cell metastases and vascular permeability? As cytokines can be exploited to evoke an immune response, is there a therapeutic index or threshold at which this may be more harmful than beneficial (i.e., in cardiac injury, as seen by Aoyagi and Matsui's paper [7])? Regarding our current multidimensional "war on cancer", there are thus many aspects as to how cytokines may be viewed in fighting this particular disease entity, but it can be additionally hypothesized that harnessing these may produce response but must be pursued with caution as their overstimulation can also cause symptoms and additional morbidity.

To put these reports into context of cancer therapy, it is important to consider how cytokines are involved in specific malignancies. First, in breast cancer, CXCL13 chemokine ligand expressed by stromal cells in B-cell follicles has been postulated to play a role in disease progression [8]. In the leukocyte chemoattractant receptor (CXCmotif) network, high expression of CXCL13-CXCR5 chemokine axis found at the mRNA level has been shown to be significantly associated with shortened disease-free survival (DFS) in ER-positive breast cancer (especially those with high nuclear grade), but associated with a more prolonged DFS in HER-2-positive breast cancer [9]. Bonecchi et al. [10] showed that CCL2 chemokines polarize tumor-associated macrophages (TAMs) and promote tumor cell proliferation and survival, guiding them to secondary metastatic sites. In breast cancer, a cytokine axis involving intracellular adhesion molecule-1 (ICAM-1), which regulates vascular permeability, is linked to expression of tumor suppressor genes [11]. Particularly, the families of suppressors of cytokine signaling (SOCS) are cytokine-inducible inhibitors of signal transduction which act via inhibition of the JAK-STAT pathway as a classical negative feedback loop, of which caveolin-1 is a significant family member [12]. Jasmin et al.[12] have shown that increased expression of caveolin-1 conversely correlates to metastasis formation. A secreted form of caveolin-1 is suggested to function as an autocrine/ paracrine growth factor, along with members of the JAK-STAT family as well as specific cytokine receptors being enriched in caveolar domains in their structure and co-precipitate with caveolin-1 [12]. Therefore the tumor microenvironment once again becomes a focus in this disease process in identifying targetable mechanisms for inhibition of tumor growth. Martinez-Outschoorn et al. [13] have shown that in vitro, coculture of fibroblasts with breast cancer cells increases their own TGF-B signaling, as well as that of numerous other cytokines including IL-

*Corresponding author: Gloria J Morris, M.D, Ph.D, Department of Medicine, Division of Hematology/Oncology, The Tisch Cancer Institute, The Mount Sinai Hospital, The Mount Sinai School of Medicine, New York, USA, E-mail: dr.gjmorris@gmail.com

Received June 25, 2012; Accepted June 27, 2012; Published June 29, 2012

Citation: Morris GJ (2012) Cytokines, Chemokines, and "Marshalling for War". J Cell Sci Ther S5:e001. doi:10.4172/2157-7013.S5-e001

Copyright: © 2012 Morris GJ. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

6, IL-8, IL-10, MIP1 α , IFN γ , RANTES, GMCSF, PAI-1. This in turn causes autophagy in adjacent associated fibroblasts, promoting breast tumor progression and metastases, with loss of Cav-1; *in vivo*, this is associated with early tumor recurrence and LN metastases [13]. Low caveolin-1 expression is even associated with interstitial lung disease as a possible pathogenic mechanism in scleroderma [14], where CXCR4 and its ligand CXCL12 (stromal cell-derived factor-1) are upregulated in the lung tissue. Expressions of CXCR7 and chemokine ligands are also detected in anaplastic astrocytomas and in glioblastoma multiforme, on both glioma cells and the vasculature [15]. Here, dampening of these cytokine network(s) may thus have downstream impact in controlling tumor growth.

A classic malignancy for which cytokine overexpression and interaction with the bone marrow microenvironment leading to malignant clonal expansion is multiple myeloma. Expressed by all myeloma cells but not by normal plasma cells, IL-1ß is a major cytokine responsible for the paracrine production of IL-6 by marrow stromal cells [16]. Mesenchymal bone marrow stromal cells from MM patients also differ from healthy donors by increased production of IL-6, IL-10, TNF-a, OPN, HGF, BAFF in response to co-culture with RPMI 8226 cells; these in turn enhance the production of sIL-6R by RPMI 8226 [16]. Lust and Donovan [17] recently showed that IL-1 antagonists inhibit paracrine IL-6 production in patients with smoldering (asymptomatic) myeloma, that this intervention can delay progression of disease to fullblown symptomatic myeloma, and therefore anti-cytokine therapies that neutralize IL-1 (i.e., IL-1Ra and low-dose dexamethasone) show promise in controlling proliferation. Furthermore, the combination of an Antibody against cell surface protein CS1 (elotuzumab) plus lenalinomide was shown to increase natural killer (NK) cells and thus increase myeloma cell kill by an associated increased IFNy, IL-2, ICAM-1, and CD25 expression [18]. However, levels of cytokines can also rise as indicator of treatment effect as well. A current study at the MD Anderson Cancer Center is measuring inflammatory cytokines by buccal swab to correlate with neurocognitive and neurosensory symptoms in multiple myeloma, and has preliminarily shown that several inflammatory markers are associated with severity of symptoms during induction therapy [19,20]. For example, sIL-R1 expression was shown to be associated with distress and sadness; sIL-6R associated with disturbed sleep, poor appetite, sore mouth; and IL-6 associated with pain, fatigue, nausea, sore mouth [20]. Whether direct cytokine intervention is a clear target or cytokine release is a result of cell death is not clear in causality. Much of the latest research in myeloma clinical therapeutic trials involves not only immunomodulatory (IMiD) therapy with drugs such as thalidomide and its derivatives -- which not only case growth arrest and/or apoptosis of multiple myeloma cells, but depressed expression of cytokines from adjacent stromal cells [21] - but also targeting of intracellular mechanisms such as inhibition of the proteosome, the use of histone deacetylase inhibitors, as well as antibodies against cell surface molecules [22,23]. Current studies evaluating their response in both first-line as well as refractory and relapsed settings are underway (http://www.cancer.gov).

In malignant melanoma, a highly immunogenic tumor, those tumors showing a brisk lymphocyte infiltrate exhibit a better overall prognosis and even the propensity for histologic regression [24]. Steele et al. [25] have shown that prokines stimulate the micro-environment and prime the immune system for fighting against tumor, with increased expression of CXCR3/CCR5 ligand chemokines (which recruit tumor-infiltrating lymphocytes (TILs)) *ex vivo* being associated with increased responsiveness to treatment in patients on several

adoptive therapy clinical trials [26]. As a classic chemokine, IL-2 has been reviewed by the Cytokine Working Group as a tool harnessed to induce remission of multiple myeloma [27,28], with the injection of peptide vaccine improving overall response rate [29]. Similar to the concept we see with the cardiac injury paper by Aoyagi and Matsui [7], however, significant toxicity has been reported with IL-2 treatment and others. In recent landmark practice-changing trials, HLA-A*0201positive patients with progressive advanced melanoma gained an improved overall survival when treated with a peptide vaccine plus ipilimumab, a human monoclonal antibody specific for the cytotoxic T-lymphocyte antigen-4 (CTLA-4) [27,30]. Ipilimumab mimics T-cell surface molecule CD28 and blocks interaction with antigen-presenting cell (APC) surface markers CD80 and 86, otherwise needed for blunting of T-cell activation, and subsequently augmenting T-cell proliferation [31]. However, patients with autoimmune diseases are at greater risk for adverse effects due to this same mechanism [27]. Furthermore, a dose-response relationship with ipilimumab can be seen in causing toxicity [32], even in treatment-naive patients receiving a higher confirmed dose [33]. Several chemokine-receptor axis antagonists are now being tested in the clinic in various tumors [34], but challenges lie in unpredictable therapeutics in animal models, and target redundance, as is thus discussed by Horuk [34].

While the immune environment and chemoattractant cytokines are one possible pathway for therapeutic intervention in disease proliferation and ultimately for malignant progression of cancer cells, myriad therapeutic target categories have also recently been reviewed to include apoptotic pathway(s), genomic mutation, angiogenesis, mechanisms of invasion and metastases [35]. Additional toxicity of chemokine-directed therapies is limiting in clinical trials and adds further challenge for therapeutic benefit. However, further research is needed to intricately and specifically identify these targets in order to develop therapeutic intervention tolerable for the host while attacking virulent and neoplastic disease.

Acknowledgement

This editorial is written in response to an invitation from the Journal of Cell Science and Therapy.

References

- Luster AD (1998) Chemokines--chemotactic cytokines that mediate inflammation. N Engl J Med 338: 436-445.
- Murphy PM (2001) Chemokines and the molecular basis of cancer metastasis. NEJM 345: 833-835.
- Nicolete R, Nicolete LDF (2011) Microencapsulated leukotrienes augment antimicrobial activity against infections. J Cell Sci Ther S5: 001.
- Logani MK, Bhopale MK, Ziskin MC (2011) Millimeter wave and drug-induced modulation of the immune system- application in cancer immunotherapy. J Cell Sci Ther S5: 002.
- Logani MK, Szabo I, Makar V, Bhanushali A, Alekseev S, et al. (2006) Effect of millimeter wave irradiation on tumor metastasis. Bioelectromagnetics 27: 258-264.
- Scholten D, Al-samman M, Sahin H, Trautwein C, Wasmuth HE (2011) CXCR3 ligands induce expression of CXCL1 (KC/murine IL8 homolog) in mouse hepatic stellate cells. J Cell Sci Ther S5: 004.
- Aoyagi T, Matsui T (2011) The cardiomyocyte as a source of cytokines in cardiac injury. J Cell Sci Ther S5: 003.
- Feng LY, Ou ZL, Wu FY, Shen ZZ, Shao ZM (2009) Involvement of a novel chemokine decoy receptor CCX-CKR in breast cancer growth, metastasis and patient survival. Clin Cancer Res 15: 2962-2970.

 Razis E, Kalogeras KT, Kotoula V, Eleftheraki AG, Nikitas N, et al. (2012) Improved outcome of high-risk early HER2 positive breast cancer with high cxcl13-cxcr5 messenger RNA expression. Clin Breast Cancer 12: 183-193.

- Bonecchi R, Locati M, Mantovani A (2011) Chemokines and cancer: a fatal attraction. Cancer Cell 19: 434-435.
- 11. Frank PG, Lisanti MP (2008) ICAM-1: role in inflammation and in the regulation of vascular permeability. Am J Physiol Heart Circ Physiol 295: H926-H927.
- Jasmin JF, Mercier I, Sotgia F, Lisanti MP (2006) SOCS proteins and caveolin-1 as negative regulators of endocrine signaling. Trends Endocrinol Metab 17: 150-158.
- Martinez-Outschoorn UE, Whitaker-Menezes D, Lin Z, Flomenberg N, Howell A, et al. (2011) Cytokine production and inflammation drive autophagy in the tumor microenvironment: role of stromal caveolin-1 as a key regulator. Cell Cycle 10: 1784-1793.
- 14. Tourkina E, Bonner M, Oates J, Hofbauer A, Richard M, et al. (2011) Altered monocyte and fibrocyte phenotype and function in scleroderma interstitial lung disease: reversal by caveolin-1 scaffolding domain peptide. Fibrogenesis Tissue Repair 4: 15.
- Berahovich RD, Walters MJ, Sullivan TJ, Kohrt HE, Karamchandani J, et al. (2012) Expression of CXCR7, CXCR4, CXCR3 and their chemokine ligands in glioblastoma. J Clin Oncol 30.
- 16. Zdzisińska B, Bojarska-Junak A, Dmoszyńska A, Kandefer-Szerszeń M (2008) Abnormal cytokine production by bone marrow stromal cells of multiple myeloma patients in response to RPMI8226 myeloma cells. Arch Immunol Ther Exp (Warsz) 56: 207-221.
- Lust J, Donovan KA (2006) Cytokine involvement in the prediction and prevention of MGUS to multiple myeloma. First AACR International Conference on Frontiers in Cancer Prevention Research, November 12-15, Abstract CS14-02.
- Balasa B, Yun R, Belmar N, Starling G, Rice A, et al. (2012) Natural killer (NK) cell activation, cytokine production, and cytotoxicity in human PBMC/ myeloma cell co-culture exposed to elotuzumab (Elo) alone or in combination with lenalidomide (Len). J Clin Oncol 30.
- 19. Inflammatory cytokines in symptom production in multiple myeloma.
- Sailors MH, Wang XS, Liu P, Johnson VE, Reuben JM, et al. (2012) Longitudinal relationship between inflammatory markers and patient-reported symptom severity during induction therapy for multiple myeloma. J Clin Oncol 30 (suppl; abstr 9083).
- 21. Bartlett JB, Dredge K, Dalgleish AG (2004) The evolution of thalidomide and its IMiD derivatives as anticancer molecules. Nat Rev Cancer 4: 314-322.
- 22. Palumbo A, Attal M, Roussel M (2011) Shifts in the therapeutic paradigm for

patients newly diagnosed with multiple myeloma: maintenance therapy and overall survival. Clin Cancer Res 17: 1253-1263.

- 23. Mikhael J, Reeder CB, Libby EN, Costa L, Mayo A, et al. (2012) A phase I/ II trial of cyclophosphamide, carfilzomib, thalidomide, and dexamethasone (CYCLONE) in patients with newly diagnosed multiple myeloma. J Clin Oncol 30.
- Oble DA, Loewe R, Yu P, Mihm MC Jr (2009) Focus on TILs: prognostic significance of tumor infiltrating lymphocytes in human melanoma. Cancer Immun 9: 3.
- 25. Steele L, Errington F, Prestwich R, Ilett E, Harrington K, et al. (2011) Proinflammatory cytokine/chemokine production by reovirus treated melanoma cells is PKR/NFkB mediated and supports innate and adaptive anti-tumor immune priming. Mol Cancer 10: 20.
- 26. Bedognetti D, Tomei S, Spivey TL, De Giorgi V, Ascierto ML, et al. (2012) Evaluation of chemokine-ligand pathways in pretreatment tumor biopsies as predictive biomarker of response to adoptive therapy in metastatic melanoma patients. J Clin Oncol 30.
- Narasimha D, Jarkowski AIII, Khushalani NI (2012) Immunotherapy in advanced melanoma. The International Journal of Targeted Therapies in Cancer 6: 37-41.
- Atkins MB, Lotze MT, Dutcher JP, Fisher RI, Weiss G, et al. (1999) High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 17: 2105-2116.
- Schwartzentruber DJ, Lawson DH, Richards JM, Conry RM, Miller DM, et al. (2011) gp100 peptide vaccine and interleukin-2 in patients with advanced melanoma. New Engl J Med 364: 2119-2127.
- Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, et al. (2010) Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363: 711-723.
- Salama AK, Hodi FS (2011) Cytotoxic T-lymphocyte-associated antigen-4. Clin Cancer Res 17: 4622-4628.
- Wolchok JD, Neyns B, Linette G, Negrier S, Lutzky J, et al. (2010) Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol 11: 155-164.
- Robert C, Thomas L, Bondarenko I, O'Day S, M D JW, et al. (2011) Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 364: 2517-2526.
- Horuk R (2009) Chemokine receptor antagonists: overcoming developmental hurdles. Nat Rev Drug Discov 8: 23-33.
- De Lartigue J (2012) Cancer research moves beyond the original hallmarks of cancer. The International Journal of Targeted Therapies in Cancer 6: 21-24.

This article was originally published in a special issue, **Cytokines** handled by Editor(s). Dr. Gino Antonio Vena, University of Bari, Italy