Journal of Leukemia
ISSN: 2329-6917

Tadmor, J Leuk 2013, 1:4
DOI; 10.4172/2329-6917.1000e103

Editorial Open Access

# Monocytes, Monocytic Myeloid Derived Suppressor Cells and Lymphoma: How Tight is the Knot of the Tie?

**Tamar Tadmor***

*Hematology Unit, Bnai-Zion Medical Center, and the Rappaport Faculty of Medicine, Technion, Institute of Technology, Haifa, Israel*

Much effort is being invested in advancing the knowledge on cancer immunology, cancer microenvironment, and their interactions both within and outside the tumor niches. In the past few years it has been recognized that tumor growth and progression, do not depend only on the biology of the malignant cells themselves but also on their interactions with a variety of other cells which play a central role in tumorigenesis [1].

Until recently, most of the experts in the field of cancer immunology could indeed be considered as "T-cell chauvinists"- as their main research interests focused on improving adoptive T-cell transfer, understanding "T-cell anergy" in cancer, and inhibiting T-regulatory cells (T-regs), a sub-population of T-cells with immunosuppressive activity. This has still remained so, until now and in the hierarchy of the cancer involved immune system, T-cells and their related subpopulations still reign supreme [2]. However, other immune cells are now being investigated and new immunosuppressive sub -populations have been discovered, including the T17, B-regulatory cells (B-regs), Myeloid Derived Suppressor Cells (MDSc) and some dendritic and natural killer cells [3,4]. Understanding their functions and interaction with tumor cells and other immunesuppresive and immune-active populations is important when trying to understand more clearly the "full picture" of tumor- immune tolerance.

In recent years, we have been interested in the role of peripheral blood monocytes in lymphoproliferative disorders in general and in lymphomas in particular, and have investigated them as a possible surrogate prognostic marker for patients with lymphoma. When we analyzed the numbers of monocytes number in the peripheral blood of patients with diffuse large B-cell lymphoma treated in our institute, we observed that high monocyte numbers correlated with adverse prognosis in these patients [5]. Together with the "Gruppo Italiano Studio Linfomi" we then validated our initial results in a large cohort of 1191 patients, and identified monocytes >630 mm3 as a cut-off value of adverse prognosis [6]. Our results are in similar to those of other groups working in this field, particularly those at the Mayo clinic, in Rochester, Minnesota demonstrating in a multivariate analysis that the Absolute Monocyte Count (AMC) was as an independent prognostic marker, with an HR-as significant as the IPI [6,7]. A similar retrospective analysis was performed by our combined Israeli-Italian groups, involving a cohort of patients with T-cell lymphomas [8] and Hodgkin disease [9] where we once again confirmed , the role of AMC as a simple and applicable prognostic marker in lymphomas, where patients with elevated AMC had a significantly less favorable prognosis [10].

Furthermore the prognostic value of AMC was also examined and reported by other groups not only in lymphomas, but also in other hematological disorders such as idiopathic myelofibrosis [11], and non- hematologic malignancies, including head and neck cancer , renal cell carcinoma, and melanoma [12,13] and Similar conclusions as for lymphomas were drawn in all these studies.

Monocytes are produced by the bone marrow, and in response to inflammatory signals, migrate to the blood and to sites of infection where they differentiate into macrophages and dendritic cells and elicit an immune response [14]. However in vitro studies demonstrated that their functions are not limited only to immune-defense, Monocytes are indeed a heterogeneous population, including a sub-population with immune-suppressive activity termed: Monocytic-Myeloid Derived Suppressor Cells (M-MDSc). These cells elicit their immunosuppressive activity utilizing different mechanisms and one of the best recognized of these is via arginase secretion which induces depletion of arginine in T-cells surrounding and in consequence T-cells are unable to generate the zeta chain and mature into active cytotoxic T-cells. The second important pathway is dependent on inducible nitric oxide synthase 2 (iNOS2). Phenotypically, monocytes are characterized being both CD14 positive/HLA DRr low/negative and mostly D16 negative and CD66b positive [15]. In our laboratory, we have examined the presence and percentage of M-MDSC in the peripheral blood of newly diagnosed patients with DLBCL. When compared to normal controls, patients with DLBCL had a statistically significant higher percentage and absolute number of peripheral blood M-DSCs at the time of diagnosis. Interestingly, when we evaluated these cells at the end of therapy, we demonstrated that the number of M-MDSc decreased to values similar to those of healthy controls [5]. In 2011, Lin et al. [16], performed the first pioneering in vitro study evaluating the mechanism in which monocytes affect the growth of non Hodgkin lymphoma cells. Monocytes had a suppressive effect on T-cell function, which was mediated through arginine metabolism, and indeed when exogenous arginine was added, this suppressive effect was over. Taking all the above into consideration, we can conclude, that it is becoming more and more evident, that the absolute monocyte count serves as a simple prognostic parameter in lymphoma, and AMC will probably be used more frequently by clinicians in the future. Studies are now in progress attempting to better understand the biological mechanisms used by monocytes and which affect their suppressive function.

## References

1. Devaud C, John LB, Westwood JA, Darcy PK, Kershaw MH (2013) Immune modulation of the tumor microenvironment for enhancing cancer immunotherapy. Oncoimmunology 2: e25961.

2. Kershaw MH, Westwood JA, Darcy PK (2013) Gene-engineered T cells for cancer therapy. Nat Rev Cancer 13: 525-541.

3. Zamarron BF, Chen W (2011) Dual roles of immune cells and their factors in cancer development and progression. Int J Biol Sci 7: 651-658.

***Corresponding author:** Tamar Tadmor, Hematology Unit, Bnai-Zion Medical Center, 47, Golomb Street, Haifa 31048, Israel, Tel: +972 48359407; Fax: +972 48359962; E-mail: tamar.tadmor@b-zion.org.il

**Received** November 06, 2013; **Accepted** November 07, 2013; **Published** November 07, 2013

**Citation:** Tadmor T (2013 )Monocytes, Monocytic Myeloid Derived Suppressor Cells and Lymphoma: How Tight is the Knot of the Tie? J Leuk 1: e103. doi:10.4172/2329-6917.1000e103

4. Olkhanud PB, Damdinsuren B, Bodogai M, Gress RE, Sen R, et al. (2011) Tumor-evoked regulatory B cells promote breast cancer metastasis by converting resting CD4â ºT cells to T-regulatory cells. Cancer Res 71: 3505-3515.

5. Tadmor T, Fell R, Polliack A, Attias D (2013) Absolute monocytosis at diagnosis correlates with survival in diffuse large B-cell lymphoma-possible link with monocytic myeloid-derived suppressor cells. Hematol Oncol 31: 325-331.

6. Tadmor T, Bari A, Sacchi S, Marcheselli L, Liardo EV, et al. (2013) Monocyte count at diagnosis is a prognostic parameter in diffuse large B-cell lymphoma: a large multicenter study involving 1191 patients, in the pre and post rituximab era. Haematologica.

7. Wilcox RA, Ristow K, Habermann TM, Inwards DJ, Micallef IN, et al. (2011) The absolute monocyte and lymphocyte prognostic score predicts survival and identifies high-risk patients in diffuse large-B-cell lymphoma. Leukemia 25: 1502-1509.

8. Bari A, Tadmor T, Sacchi S, Marcheselli L, Liardo EV, et al. (2013) Monocytosis has adverse prognostic significance and impacts survival in patients with T-cell lymphomas. Leuk Res 37: 619-623.

9. Tadmor T, Marcheselli L, Aviv A, Pozzi S, Liardo EV, et al. (2013) The addition of lymphocyte/monocyte ratio (LMR) to the international prognostic score for Hodgkin lymphoma identifies low risk patients with adverse prognosis. Haematologica S2.

10. Tadmor T (2013) Does monocyte count have prognostic significance in cancer? Leuk Res 37: 1193-1194.

11. Elliott MA, Verstovsek S, Dingli D, Schwager SM, Mesa RA, et al. (2007) Monocytosis is an adverse prognostic factor for survival in younger patients with primary myelofibrosis. Leuk Res 31: 1503-1509.

12. Schmidt H, Bastholt L, Geertsen P, Christensen IJ, Larsen S, et al. (2005) Elevated neutrophil and monocyte counts in peripheral blood are associated with poor survival in patients with metastatic melanoma: a prognostic model. Br J Cancer 93: 273-278.

13. Hermann GG, Geertsen PF, von der Maase H, Zeuthen J (1991) Interleukin-2 dose, blood monocyte and CD25+ lymphocyte counts as predictors of clinical response to interleukin-2 therapy in patients with renal cell carcinoma. Cancer immunology, immunotherapy CII 34: 111-114.

14. Poplack DG, Bonnard GD, Holiman BJ, Blaese RM (1976) Monocyte-mediated antibody-dependent cellular cytotoxicity: a clinical test of monocyte function. Blood 48: 809-816.

15. Marigo I, Dolcetti L, Serafini P, Zanovello P, Bronte V (2008) Tumor-induced tolerance and immune suppression by myeloid derived suppressor cells. Immunol Rev 222: 162-179.

16. Lin Y, Gustafson MP, Bulur PA, Gastineau DA, Witzig TE, et al. (2011) Immunosuppressive CD14+HLA-DR(low)/- monocytes in B-cell non-Hodgkin lymphoma. Blood 117: 872-881.