Biohelikon: Immunity and Diseases, 2013 1:1

Editorial

Multiple Myeloma and its role in immunosupression

Ana Flávia F. R. Nardy[1], Juliana Echevarria Lima[1], Angelo Maiolino[2], and Alexandre Morrot[1*]

[1] Institute of Microbiology, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

[2] Hematology Service, University Hospital Clementino Fraga Filho, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

[*] Corresponding author, Email: morrot@micro.ufrj.br

Abstract

Multiple Myeloma (MM) is a plasma cell malignancy characterized by immunosuppression and increase of susceptibility to several infections, which considerably decreases the survival rate of patients. The immunosuppression of anti-tumor protective responses is a common characteristic to a variety of neoplasias, and it involves the immune responses subversion, especially those elicited by dendritic cells (DCs). The development of an immunosuppressive niche by the tumor is suggested to represent an important mean to induce DCs differentiation towards a tolerogenic profile. Tolerogenic DCs are known to induce $CD8^+$ regulatory T cells, a subset of $CD8^+$ T cells which has recently received more attention since its original discovery decades ago. These events started to be unveiled and may act as a key mechanism responsible for the impaired immune functions seen in MM. In this editorial, we focus on the compromised anti-tumor immune responses against MM on the basis of DCs activity modulation and their role in $CD8^+$ Treg induction.

Keywords

Multiple Myeloma, Dendritic cells, $CD8^+$ Treg cells

Multiple Myeloma (MM) is a B-cell malignancy characterized by the clonal expansion of plasma cells in the bone marrow (BM). It evolves from a premalignant and asymptomatic condition known as monoclonal gammopathy of undetermined significance (MGUS) [1]. Main clinical manifestations found in MM patients include hypercalcemia, osteolytic lesions, renal dysfunction, peripheral neuropathy and hyperviscosity, a condition caused by the increase of blood viscosity due to the excess of M protein (antibody or part of it found at high concentrations of urine and/ or blood of patients with plasma cell tumors) [2]. Cell-to-cell contact and soluble factors provided by bone marrow stromal cells (BMSCs) are essential to proliferation and survival of malignant plasma cells, playing a vital role in the pathogenesis of the disease [3,4]. Immune dysfunction is a striking characteristic of MM, that, besides promoting tumor growth, can lead to infections representing the main cause of morbidity and mortality among MM patients [5,6]. Here, we briefly discuss some immunological aspects trough which MM cells could subvert the anti-tumor responses.

The effects of MM modulation over the BM microenvironment can also target host immune effectors. Malignant plasma cells released cytokines and growth factors in BM, altering and leading an impairment of the cell differentiation from hematopoietic stem and progenitor cells [7]. Common myeloid progenitor cells (CMPs) and Common lymphoid progenitor cells (CLPs) are affected by malignant B-cell BM infiltration [7], correlating this effect with the immune dysfunction presented by MM patients.

DCs are the most important antigen-presenting-cells. They are responsible for capturing and presenting antigens on major histocompatibility complex (MHC) molecules to naïve T cells, efficiently initiating adaptative immune responses [8]. DCs are heterogeneous cell group and they are subdivided in two main groups: conventional and plasmacytoid DCs. The conventional DCs are derived from CMP, directly, or differentiate from a monocyte precursor [9]. Moreover, CLPs produced only a few conventional DCs and plasmacytoids DCs [10]. Based on their activation state, DCs may exhibit an immature (iDCs) or a mature phenotype (mDCs). iDCs show high phagocytic activity and express low levels of costimulatory molecules, such as CD80 and CD86, with consequent reduced ability to present antigens. These cells are known to induce tolerance in terms of T-cell anergy or depletion and by induction of regulatory T cells (Treg) [11,12]. Conversely, some studies point out a role of mDCs in T-cell anergy induction [13]. The upregulation of HLA-DR and the costimulatory molecules are critical steps for the maturation process into mDCs.

DCs play a key role in cancer immunity through their exceptional capacity to initiate T cell responses. Nevertheless, tumors can manipulate other resident cells types in the tumor microenvironment, including DCs, in order to support their metastasis and evasion from immune surveillance [14]. Kukreja *et al.* demonstrated that human MM cells lines cultured with DCs show an enhancement of clonogenicity [15]. Besides, the BM microenvironment in MM

is enriched with a multitude of cytokines such as interleukin-6 (IL-6), interleukin-10 (IL-10) tumor-necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), and vascular endothelial growth factor (VEGF), some of them induce an impairment of DCs differentiation and maturation [16,17]. Hayashi *et al.* demonstrated that serum derived from the bone marrow of MM patients inhibits DC generation; and that anti-VEGF and anti-IL-6 antibodies block this inhibitory effect. In addition, DCs loaded with tumor lysates from MM cells show lower phenotypic maturation and abnormal T cell stimulatory ability [18]. Furthermore, the development of an immunosuppressive niche by the tumor is suggested to represent an important mechanism to stimulate DC differentiation towards a tolerogenic profile. Characteristically, cytokines such as IL-10 and TGF-β are known to induce tolerogenic DCs *in vitro*. A hallmark of tolerogenic DCs is their ability to induce Treg cells; not only the classical $CD4^+CD25^+FoxP3^+$ phenotype, but also the not fully characterized $CD8^+$ regulatory T cells ($CD8^+$ Treg) [19]. Fiore *et al.* (2005) demonstrated that DCs stimulated with necrotic primary myeloma cells presented lower capacity to activate autologous T cells. T cells elicited by DCs, previously, stimulated by necrotic primary myeloma cells showed reduced proliferation and IFN-γ, but release higher levels of IL-10. These results suggested that T cells activated by DCs, previously, stimulated by necrotic primary myeloma cells, exhibit a different phenotype[20]. In 2006, Banerjee *et al.* that DCs derived of peripheral blood monocytes obtained from MM patients induced an expansion of $CD4^+FoxP3^+$ *in vitro* and *in vivo*[21].

Similar to their $CD4^+$ counterpart $CD8^+$ Treg either originate from thymus or arise in the periphery under certain conditions [22]. In further analogy to $CD4^+$ Treg several subpopulations, such as $CD8^+CD122^+$ Treg and $CD8^+CXCR3^+$ Treg [23,24,25], and a large number of suppressive mechanisms, including release of IL-10, induction of anergy and contact dependent mechanism, have been described [26]. Whereas the role of $CD4^+$ Treg in cancer has been widely studied, little is known about $CD8^+$ Treg and their role in immune responses against tumors, especially in MM. Recently, Raja *et al.* described an increase in the functionally suppressive $CD8^+$ T lymphocytes ($CD8^+CD25^{hi}$) in newly-diagnosed MM patients. Importantly, the expression of FoxP3 in these cells was also enhanced. This cellular subpopulation is believed to contribute for immune dysfunction seen in MM [27]. Also, these cells could have their function altered by the tumor microenvironment since under non-inflammatory conditions murine osteoclasts induce $FoxP3^+CD8^+$ T-cells able to suppress bone resorption [28]. Hence, further analysis in this sense need to be done, since stimulation of osteoclastogenesis and inhibition of osteoblastogeneis is a remarkable characteristic in MM, leading to osteolytic lesions.

At the present, there are still several aspects to be elucidated about cellular and molecular bases of the immune modulation during anti-MM responses. However, an important event concerning these responses is that tumor microenvironment dampens the host immune control, mainly affecting the normal DCs functions and differentiation. The strict knowledge of the roles that govern these inadequate functions and their consequences, especially about how defectives DCs interact with T cells, is essential to set up the basis for generation of new immunotherapies, designed to improve the efficiency of the responses against MM.

References

1. Kyle RA, Rajkumar SV: Multiple myeloma. Blood 2008, 111: 2962-2972
2. Kyle RA, Rajkumar SV: Multiple myeloma. N Engl J Med 2004, 351: 1860-1873
3. Roodman GD: New potential targets for treating myeloma bone disease. Clin Cancer Res 2006, 12: 6270s-6273s
4. Ribatti D, Nico B, Vacca A: Importance of the bone marrow microenvironment in inducing the angiogenic response in multiple myeloma. Oncogene 2006, 25: 4257-4266
5. Pratt G, Goodyear O, Moss P: Immunodeficiency and immunotherapy in multiple myeloma. Br J Haematol 2007, 138: 563-579
6. Pessoa de Magalhães RJ, Vidriales MB, Paiva B, Fernandez-Gimenez C, García-Sanz R, et al.: Analysis of the immune system of multiple myeloma patients achieving long-term disease control by multidimensional flow cytometry. Haematologica 2013, 98: 79-86
7. Bruns I, Cadeddu RP, Brueckmann I, Fröbel J, Geyh S, et al.: Multiple myeloma-related deregulation of bone marrow-derived CD34(+) hematopoietic stem and progenitor cells. Blood 2012, 120: 2620-2630
8. Banchereau J, Steinman RM: Dendritic cells and the control of immunity. Nature 1998, 392: 245-252
9. Liu K, Nussenzweig MC: Origin and development of dendritic cells. Immunol Rev 2010, 234: 45-54
10. Sathe P, Vremec D, Wu L, Corcoran L, Shortman K: Convergent differentiation: myeloid and lymphoid pathways to murine plasmacytoid dendritic cells. Blood 2013, 121: 11-19
11. Gabrilovich DI, Nagaraj S: Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol 2009, 9: 162-174
12. Hubo M, Trinschek B, Kryczanowsky F, Tuettenberg A, Steinbrink K, et al.: Costimulatory molecules on immunogenic versus tolerogenic human dendritic cells. Front Immunol 2013, 4: 82
13. Gregori S, Tomasoni D, Pacciani V, Scirpoli M, Battaglia M, et al.: Differentiation of type 1 T regulatory cells (Tr1) by tolerogenic DC-10 requires the IL-10-dependent ILT4/HLA-G pathway. Blood 2010, 116: 935-944
14. Gabrilovich D: Mechanisms and functional significance of tumour-induced dendritic-cell defects. Nat Rev Immunol 2004, 4: 941-952
15. Kukreja A, Hutchinson A, Dhodapkar K, Mazumder A, Vesole D, et al.: Enhancement of clonogenicity of human multiple myeloma by dendritic cells. J Exp Med 2006, 203: 1859-1865
16. Ratta M, Fagnoni F, Curti A, Vescovini R, Sansoni P, et al.:Dendritic cells are functionally defective in multiple myeloma: the role of interleukin-6. Blood 2002, 100:230-237
17. Yang DH, Park JS, Jin CJ, Kang HK, Nam JH, et al.: The dysfunction and abnormal signaling pathway of dendritic cells loaded by tumor antigen can be overcome by neutralizing VEGF in multiple myeloma. Leuk Res 2009, 33: 665-670
18. Hayashi T, Hideshima T, Akiyama M, Raje N, Richardson P, et al.: Ex vivo induction of multiple myeloma-specific cytotoxic T lymphocytes. Blood 2003, 102: 1435-1442
19. Maldonado RA, von Andrian UH: How tolerogenic dendritic cells induce regulatory T cells. Adv Immunol 2010, 108: 111-165
20. Fiore F, Nuschak B, Peola S, Mariani S, Muraro M, et al.: Exposure to myeloma cell lysates affects the immune competence of dendritic cells and favors the induction of Tr1-like regulatory T cells. Eur J Immunol 2005, 35: 1155-1163
21. Banerjee DK, Dhodapkar MV, Matayeva E, Steinman RM, Dhodapkar KM: Expansion of FOXP3high regulatory T cells by human dendritic cells (DCs) in vitro and after injection of cytokine-matured DCs in myeloma patients. Blood 2006, 108: 2655-2661

22. Cosmi L, Liotta F, Lazzeri E, Francalanci M, Angeli R, et al.: Human CD8+CD25+ thymocytes share phenotypic and functional features with CD4+CD25+ regulatory thymocytes. Blood 2003, 102: 4107-4114
23. Suzuki H, Kundig TM, Furlonger C, Wakeham A, Timms E, et al.: Deregulated T cell activation and autoimmunity in mice lacking interleukin-2 receptor beta. Science 1995, 268:1472–1476.
24. Rifa'i M, Kawamoto Y, Nakashima I, Suzuki H: Essential roles of CD8+CD122+ regulatory T cells in the maintenance of T cell homeostasis. J Exp Med 2004, 200: 1123-1134
25. Shi Z, Okuno Y, Rifa'i M, Endharti AT, Akane K, et al.: Human CD8+CXCR3+ T cells have the same function as murine CD8+CD122+ Treg. Eur J Immunol 2009, 39: 2106-2119
26. Dinesh RK, Skaggs BJ, La Cava A, Hahn BH, Singh RP: CD8+ Tregs in lupus, autoimmunity, and beyond. Autoimmun Rev 2010, 9: 560-568
27. Muthu Raja KR, Kubiczkova L, Rihova L, Piskacek M, Vsianska P, et al.: Functionally suppressive CD8 T regulatory cells are increased in patients with multiple myeloma: a cause for immune impairment. PLoS One 2012, 7: e49446
28. Buchwald ZS, Kiesel JR, DiPaolo R, Pagadala MS, Aurora R: Osteoclast activated FoxP3+ CD8+ T-cells suppress bone resorption in vitro. PLoS One 2012, 7: e38199