Macrophages and myeloid derived suppressor cells-independent dysregulation of thymopoiesis by CCL2 in acute myeloid leukemia

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In cancer-affected patients and experimental mouse models, the CCL2 chemokine is well documented to directly stimulate the proliferation and migration of tumor cells. It also attracts type 2 macrophages and myeloid derived suppressor cells that abrogate intra-tumor T-cell responses and facilitate cancer cells growth and metastasis. Accumulation of CCL2 has been found in the sera of patients suffering from acute myeloid leukemia (AML), however, its functions in disease development remain to be determined. Using an AML experimental mouse model, we have recently shown increased levels of CCL2 in the sera and thymi of mice. CCL2 blockade in vivo resulted in prolonged leukemic mice survival, lower tumor burden and enhanced anti-leukemic responses. In this work, we highlighted a surprising role of CCL2 during AML which affects thymic function in the absence of macrophages and myeloid derived suppressor cells recruitment.

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Introduction

The MCP-1 (monocyte chemoattractant protein-1) or CCL2 (C-C motif ligand 2) protein belongs to the C-C chemokine family. This chemokine is secreted by different cellular sources: monocytes, astrocytes, fibroblasts, epithelial, endothelial, smooth muscle and microglial cells. Its non-glycosylated form encompasses a molecular mass of 7-8 kDa and has been described as a chemoattractant molecule for monocytes/macrophages, dendritic and memory T cells, all expressing its main receptor CCR2 [1]. Beyond this function, CCL2 has also been attributed other roles in cell proliferation regulation, autophagy, differentiation and death in inflammatory diseases [2].

Exacerbated CCL2 production in vivo is well described in cancer-affected patients and experimental mouse models. CCL2 secretion by human prostate cancer cells promotes their proliferation in vitro through CCR2 binding [3-5]. CCL2 produced in vitro by bone marrow endothelial and stromal cells also recruits myeloma and prostate cancer cells suggesting a role in bone marrow homing and metastasis (figure 1) [3-7]. In vivo, the CCL2 release by tumor cells favors angiogenesis and tumor growth through the attraction of blood circulating CD11b+ myeloid cells (figure 1) [8, 9]. Among them, myeloid derived suppressor cells (MDSC), originating from the bone marrow, infiltrate the tumors and suppress anti-tumor specific T cells responses by different mechanisms: L-arginine deprivation, release of reactive oxygen species and peroxynitrite production in the tumor microenvironment [10]. These mediators hamper T cells
activation and proliferation or induce their death by apoptosis [10]. Similarly, tumor-associated macrophages that differentiate from CCL2-attracted monocytes inhibit intra-tumor T-cell responses through the expression of arginase-1 leading to deprivation of extracellular L-arginine. They also express ligands for death receptors or immunosuppressive cytokines as IL-10 and TGF-β [11] that abrogate Th1 responses. Their production of growth factors (V-EGF, EGF…), ornithine and matrix metalloproteinases facilitate angiogenesis, tumor progression and metastasis [11].

Acute myeloid leukemia (AML) is a clonal disorder originating from the excessive proliferation of maturation-defective myeloid progenitor/precursor cells. Erythrocytes, granulocytes, monocytes or platelets lineages can be affected and the accumulation of leukemic cells in the bone marrow results in hematopoiesis dysfunction. High levels of cytokines and chemokines, including CCL2, are found in the sera of AML-affected patients [12-14]. In vitro studies have indicated that CCL2 amounts secreted by leukemic cells are not required for their proliferation but needed for their migration [13, 14]. A study also reports that co-expression of CCL2 and its CCR2 receptor on AML cells favors their recruitment in extra-medullary sites [13]. However, as the CCR2 receptor is not expressed by all leukemic cells in patients [13, 14], other roles can be ascribed to CCL2 during AML and remain to be explored.

We recently investigated the role of the CCL2 chemokine in an experimental AML mouse model. Disease was induced by injection of a murine AML cell line. Mice that received the leukemic cells presented increasing CCL2 protein rates in the sera during AML development [15]. Neutralizing CCL2 in vivo resulted in an enhanced mice survival, a lowered tumor burden, reduced organs invasion and an increased anti-leukemic T-cell response [15]. As observed in patients, we demonstrated that CCR2 was expressed by about 32% leukemic cells (unpublished data). Blocking CCL2 production in leukemic immune-deficient (NOD/SCID) mice did not abrogate the AML cells proliferation or their organ infiltration (unpublished data).

Interestingly, we showed that thymic CCL2 mRNA and proteins levels also increased during AML and that leukemic mice presented an accelerated thymic involution resulting in a peripheral T-cell lymphopenia [15]. As AML patients...
present variable circulating T cells numbers and reduced thymic emigrant T lymphocytes, we assessed the role of CCL2 in thymic function \[16\]. Using thymectomized leukemic mice and CCL2 blockade in vivo, we showed no prolonged mice survival nor improved anti-leukemic T-cell responses without thymocytes revealing that CCL2 was affecting their differentiation in T lymphocytes (figure 1).

We next examined whether MDSC or macrophages could be attracted to the thymus and suppress thymocytes activation, proliferation or favor their death. We found no thymic recruitment of CD11b⁺ myeloid cells during AML but we described an up-regulation of the CCR2 expression on thymocytes (figure 1) \[15\]. A recent study indicates that thymic CCL2 expression increases upon inflammatory/infectious conditions and facilitates the entry of CCR2⁺ activated T cells \[17\]. It was shown that activated T lymphocytes can re-enter the thymus during infection where they constitute a memory pool or eliminate foreign antigens \[18\]. In homeostatic state and lymphopenic hosts, these mature T lymphocytes exert different functions in the thymus: maintenance of the medullary epithelial cells survival, contribution to positive selection through their MHC molecules, participation to negative selection through the antigens they present, or killing of the antigen-presenting cells they recognized \[18-20\]. Thymic CCL2 expression was also recently described to contribute to antigen tolerance through the recruitment of thymic SIRPα⁺ and plasmacytoid dendritic cells \[21, 22\]. Therefore, our current investigations are now focused on identifying mechanisms by which the CCL2/CCR2 signaling pathway could impair the thymocytes differentiation in the course of AML. Our findings will give new insights in the processes leading to AML-associated T-cell defects.

Thus, we showed that, although CCL2 has not been documented to exert chemotactic functions in the thymus in homeostatic state, its accumulation in infectious/inflammatory conditions could have potent effects on thymic function.

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Conflict of Interest

None.

References


