Biochimica et Biophysica Acta 1846 (2014) 392–404

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbacan

Review

Cellular immunotherapy in multiple myeloma: Lessons from preclinical models

M. Binsfeld [a], K. Fostier [b], J. Muller [a], F. Baron [a,c], R. Schots [b], Y. Beguin [a,c], R. Heusschen [a,*,1], J. Caers [a,c,1]

[a] Laboratory of Hematology, GIGA-Research, University of Liège, Avenue de l'Hôpital 1, 4000 Liège, Belgium
[b] Department of Clinical Hematology, Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium
[c] Department of Medicine, Division of Hematology, University and CHU of Liège, Liège, Belgium

ARTICLE INFO

Article history:
Received 12 May 2014
Received in revised form 31 July 2014
Accepted 2 August 2014
Available online 7 August 2014

Keywords:
Multiple myeloma
Mouse models
Immunotherapy
Transplantation
Adoptive transfer
Vaccination

ABSTRACT

The majority of multiple myeloma patients relapse with the current treatment strategies, raising the need for alternative therapeutic approaches. Cellular immunotherapy is a rapidly evolving field and currently being translated into clinical trials with encouraging results in several cancer types, including multiple myeloma. Murine multiple myeloma models are of critical importance for the development and refinement of cellular immunotherapy. In this review, we summarize the immune cell changes that occur in multiple myeloma patients and we discuss the cell-based immunotherapies that have been tested in multiple myeloma, with a focus on murine models.

Contents

* Corresponding author. Tel.: +32 43 664915.
E-mail address: r.heusschen@ulg.ac.be (R. Heusschen).
[1] RH and JC are co-senior authors.

http://dx.doi.org/10.1016/j.bbcan.2014.08.001
0304-419X/

1. Introduction

Multiple myeloma (MM) is a clonal B-cell malignancy characterized by an accumulation of malignant plasma cells in the bone marrow, and the presence of a monoclonal protein in the serum and/or urine, decreased normal immunoglobulin levels and lytic bone disease [1]. Standard treatment of MM in patients up to the age of 65 years consists in an initial induction based on the administration of immunomodulatory agents (thalidomide or lenalidomide) or the proteasome inhibitor bortezomib, combined with chemotherapy or dexamethasone, followed by autologous stem cell transplantation (auto-SCT) and consolidation/maintenance therapy. Elderly patients benefit from combination therapy including novel agents, followed by prolonged maintenance therapy until disease progression. However, despite improvement of results with current drug therapies, the vast majority of patients relapse due to the appearance or persistence of multidrug-resistant plasma cell clones.

Immunotherapy is a promising field in cancer research and includes both non-cellular immunotherapy and cell-based immunotherapy. Different forms of cellular immunotherapy with potent anti-myeloma activity have been investigated and validated in pre-clinical in vitro and in vivo models. In fact, immunotherapy as a novel treatment modality might offer long-term disease control in MM patients. However, numerous challenges have to be addressed before immunotherapy can be broadly used to treat MM patients, such as the identification of an optimal target antigen for vaccination strategies, the occurrence of myeloma resistance and the general immunosuppressive nature of multiple myeloma which hampers immune cell-based treatment approaches. Thus, addressing these challenges in murine models is of great interest.

Several immunocompetent murine models of MM have been established and have been of value for the preclinical investigation of MM immunotherapy (Table 1). MOPC315 and similar cell lines (J558, HOPC, …) are plasmacytoma-resembling transplantable myeloma cells that were isolated from granulomas obtained after injecting mineral oil in the peritoneum of Balb/c mice [2]. The 5TMM model comprises the transplantable 5T2MM and 5T33MM cell lines and the 5TGM1 subclone [3,4]. This model originates from aging C57BL/KaLwRij mice, an inbred substrain of C57 black mice, in which a small proportion of the animals spontaneously develop a myeloma-like disease with a primary localization of myeloma cells in the bone marrow, resulting in anemia and bone lesions, closely resembling the human counterpart. Conversely, immunodeficient models have been developed to assess the effectiveness of cellular immunotherapy in xenograft models of human MM (Table 2). There is currently no ideal myeloma model that accurately reflects all aspects of the disease and each model has its advantages and limitations. Therefore, it is important that investigators chose adequate models for answering their questions.

In this review, we first summarize the general immune alterations observed in multiple myeloma. We provide an overview of the different cellular immunotherapeutic strategies that have been tested in murine MM models, i.e. transplantation-based and adoptive transfer-based immunotherapy and dendritic cell vaccination, and describe how immune cells may be manipulated to overcome the MM-related immune suppressive effects in order to eradicate the malignant clone. Relevant findings from in vitro studies as well as clinical studies are also discussed.

2. Immune cell alterations in multiple myeloma

Impairment of the immune system is a well-known phenomenon associated with MM. It is involved in MM progression and responsible for an increased risk of infections and secondary malignancies in myeloma patients. On the one hand, this immune alteration is caused by the suppression of normal hematopoiesis through replacement of the normal bone marrow by malignant plasma cells. However, suppression of normal hematopoiesis can also occur at a relatively low MM infiltration rate due to MM-related microenvironmental changes that impair the proliferation and function of the $CD34^+$ hematopoietic stem and progenitor cells [5].

Moreover, the immune system is actively suppressed by myeloma cells and through their interaction with the microenvironment. This immune suppression is related to several mechanisms including secretion of immunosuppressive factors and recruitment of immune suppressive cells by MM cells, deficient antigen processing and presentation by host antigen-presenting cells and inhibition of activated T cells via expression of co-inhibitory molecules by the malignant cells [6]. Both the number and the activity of several immune effector cells (Fig. 1) are affected by immune suppression in MM and this partially explains the anti-neoplastic activity of non-cellular immunotherapies, such as immunomodulatory drugs, which are able to revert immune effectors to their physiological functions [7–12].

2.1. T cells

T lymphocytes, i.e. CD4 helper T cells and CD8 cytotoxic T cells (CTLs), play a crucial role in anti-tumor immunity. In myeloma patients, several CD4 and CD8 T-cell abnormalities have been described, most frequently a decrease of CD4 T cells [13–18]. Specifically, Schutt et al. reported reduced levels of memory CD4 T cells ($CD4^+CD45RO^+$), as well as activated $CD3^+HLA\text{-}DR^+$ T cells in the blood of MM patients [18]. The decrease in total CD4 T cells was associated with a reduced survival, an advanced disease stage and an increased relapse probability [15,16]. In addition, viral antigen-specific CTL response is impaired in MM patients, which might partially explain the limited success of anti-myeloma immunizations [19].

Within the CD4 subset, different T helper (Th) subsets can be distinguished based on the secretion of distinct cytokine profiles. Th1 and Th2 cells cross-regulate each other's development, and the balance between these cell types is important for an efficient immune response. Th1 cells produce interferon (IFN)-γ and interleukin (IL)-2 and play a role in cell-mediated immunity, while Th2 cells promote humoral immunity and produce IL-4, IL-5, IL-6, IL-10, IL-13 and IL-25 [20,21]. In myeloma patients, abnormal Th1/Th2 ratios have been reported [17,20,22]. Sharma et al. describe a polarization towards Th2 cytokines along with Th1 suppression [22] while others report a decrease of Th2 cells, leading to an increased Th1/Th2 ratio [17]. The observations of Sharma et al. are supported by findings in a murine MM model in which anti-myeloma activity of Th1 cells was reported [23], and by observations suggesting an attenuation of Th1 responses induced by MM cells [24]. However, additional studies are needed to confirm these findings.

Th17 cells, an IL-17 secreting subset of CD4 T cells, could also play an important role in MM. The MM-secreted cytokines transforming growth factor (TGF)-β and IL-6 induce the differentiation of Th17. Subsequently, IL-17 promotes MM cell growth, resulting in a positive feedback loop [25]. Indeed, increased proportions of Th17 cells have been observed in blood and bone marrow from MM patients. This increase could also be triggered by dendritic cells [26,27].

Several of these T-cell alterations might occur due to the excessive production of TGF-β by MM cells, which suppresses T-cell responses through the inhibition of the IL-2 autocrine pathway in these cells [8,28]. In addition, Gorgun et al. demonstrated that MM cells induce the expression of the suppressor of cytokine signaling (SOCS) 1 in CD4 and CD8 T cells, which is a negative regulator of IL-2, IFN-γ and IL-6 signaling, thus attenuating Th1 and CTL responses [12,24].

Another T-cell suppressive mechanism involves the programmed death 1 (PD-1) coinhibitory molecule, a transmembrane protein expressed on activated T cells that is involved in T-cell homeostasis. Binding of PD-1 to its ligand PD-L1 (B7-H1) generates an inhibitory signal, resulting in a reduction of T-cell proliferation and production of cytokines, which counterbalances T-cell stimulatory signals [29]. In contrast to normal plasmocytes, myeloma cells express PD-L1 [29–31] and T cells from MM patients express increased levels of PD-1 [30].