Biochimica et Biophysica Acta 1862 (2016) 368–380

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Myeloid derived suppressor cells in inflammatory conditions of the central nervous system☆

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ARTICLE INFO

Article history:
Received 14 May 2015
Received in revised form 16 October 2015
Accepted 19 October 2015
Available online 23 October 2015

Keywords:
Multiple sclerosis
Spinal cord injury
Autoimmunity
Neuroregeneration
Cell therapy
T cell suppression

ABSTRACT

The knowledge of the immune system elements and their relationship with other tissues, organs and systems are key approximations for the resolution of many immune-related disorders. The control of the immune response and/or its modulation from the pro-inflammatory to the anti-inflammatory response is being deeply studied in the field. In the last years, the study of myeloid-derived suppressor cells (MDSCs), a group of immature myeloid cells with a high suppressive activity on T cells has been extensively addressed in cancer. In contrast, their role in neuroimmune diseases is far from being totally understood. In this review, we will summarize data about MDSCs coming from the study of neuroinflammatory diseases in general and their potential role in multiple sclerosis, in order to introduce the putative use of this extraordinary promising cell type for future cell-based therapies.
This article is part of a Special Issue entitled: Neuro Inflammation edited by Helga E. de Vries and Markus Schwaninger.

1. Introduction

Inflammation is one of the most complicated processes in the human body, and the promoting and inhibiting mechanisms controlling them are significant players in the pathogenesis of various diseases. Generally, acute inflammation is a protective reaction against disease. In contrast, in chronic situations, the inflammatory process persists, with periodic reactivations [1]. The paradigm of a chronic inflammatory insult affecting the central nervous system (CNS) is multiple sclerosis (MS), in which the immune system exacerbation results in leukocyte infiltration, blood–brain barrier (BBB) disruption, demyelination and axonal damage [2]. In most patients, the disease starts with a relapsing–remitting course (RRMS), which is followed after several years by a secondary progressive phase (SPMS). Patients with primary progressive disease (PPMS) miss the relapsing and remitting stage and start with uninterrupted progression from disease onset [2]. In the case of RRMS, its clinical course may imply the existence of specific control mechanisms to modulate the immune response or the evolution from a pro- to an anti-inflammatory scenario [3]. Moreover, although with differences in lesion load between the RRMS and the progressive forms, the white matter of all MS patients presents demyelinating plaques [4]. In the active lesions, myelin is actively destroyed but still has the possibility of endogenous repair, i.e. partial remyelination. In contrast, in chronic lesions, the molecular environment of the demyelinated area changes and remyelination, when occurs, is restricted to the periplaque area and totally absent within the plaque itself [5]. This challenging scenario in a given area of the white matter points to the existence of molecular or cellular factors that trigger the evolution from a theoretically positive environment for remyelination to the impossibility of myelin recovery. In both the global clinical course and the specific white matter destruction, it is clear the necessity of regulatory processes that controls the transition from the pro- to the anti-inflammatory environment, i.e. the modulation from a destroying to a repairing environment.

In the last years, the concept of immune system modulation has gained importance within the field of neuroimmunology [6]. $CD4^+$ T-cells can acquire different functional phenotypes depending on the molecular context in which an antigen is presented by antigen presenting cells (APCs). All of these activity states are specialized in producing different groups of mediators and in recruiting different sets of immune cells, with inflammatory or anti-inflammatory consequences. The inflammatory phenotype T-helper 1 (Th1), is associated with the production of IFN-γ and often TNF-α, as well, with tissue damaging consequences. In contrast, Th2 phenotype is classically related to IL-4, IL-10 and TGF-β and has been traditionally associated to tissue repair. This classical distinction between Th1 (pro-inflammatory) and Th2 (anti-inflammatory) or activator versus regulatory cells (Th versus

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http://dx.doi.org/10.1016/j.bbadis.2015.10.015
0925-4439/

Treg) is being actively extended to other myeloid cell types: inflammatory and regulatory dendritic cells (DCs) [7], N1 and N2 neutrophils [8], and M1 and M2 macrophages [9]. The latter can be polarized in vitro into the M1 proinflammatory phenotype after stimulation with IFN-γ and lipopolysaccharide (LPS). The alternatively activated M2 phenotype (M2 macrophages) is further classified as M2a or wound-healing phenotype after exposure to IL-4 or IL-13, as M2b after exposure to immune complexes in combination with IL-1A or Toll-like receptor agonists, and as M2c after stimulation with IL-10 and glucocorticoids [10]. Moreover, one activity state of a single cell type can modify the phenotype of the surrounding cells. For instance, the Th1 or Th2 phenotype of $CD4^+$ cells strongly stimulates the activation of control microglia/macrophages towards a pro-inflammatory or anti-inflammatory activity state, respectively (for an extensive review see: [6]). Hence, a very precise network comprised by several cell types should exist in order to coordinate different aspects of the immune system response.

In the last years, myeloid-derived suppressor cells (MDSCs) have emerged as a new cell type with a pivotal role in the control of the immune response [11]. Recent data has shown that, in the context of neuroimmunology, MDSCs participate not only as powerful controllers of T cell activity, but also as important modulatory agents for the recovery from an immunological insult. Coming from the field of cancer research, MDSCs may become promising therapeutic targets in several neuroimmunological diseases, including MS. In this review, the recent data about the MDSC role in MS and other neuroimmune pathologies will be described, highlighting their potential therapeutic use for speeding up the resolution of an inflammatory episode.

2. MDSCs: general concepts

2.1. Origin and classification

MDSCs are a heterogeneous population of myeloid cells comprised by myeloid progenitors and immature myeloid cells (IMCs) with a potent ability to suppress different aspects of the immune response. The different cell types forming the heterogeneous population of MDSCs are originated during the myelopoiesis, which takes place in the bone marrow. During this process, haematopoietic stem cells differentiate into common myeloid progenitor cells and IMCs in response to a complex molecular network (for a review see [12]). In healthy conditions, IMCs represent about 20–30% of normal bone marrow and are able to migrate to different peripheral organs and differentiate into macrophages, DCs or granulocytes [12]. However, in pathological conditions, IMCs are prevented from differentiating into mature cells, remaining in an undifferentiated phenotype. When this immaturity is present together with a high immunosuppressive capacity, they are called MDSCs [13].

The heterogeneity of MDSCs created debate and difficulties about their classification. Initially, MDSCs in mice were determined by the co-expression of the myeloid-cell lineage differentiation antigen Gr-1 and CD11b, as well as the lack of expression of typical markers of mature macrophages and DCs [14]. Further studies described that specific antibodies for Gr-1 bind to two different epitopes: Ly-6G and Ly-6C, which can be detected separately [15]. The nomenclature is due to the fact that Ly-6G epitope has been firstly described in granulocytes [16] whereas Ly-6C molecule is known to be mainly expressed on monocyte-derived cells [17]. Currently, MDSCs have been classified in mice into two groups based on the level of expression of Ly-6G and Ly-6C: granulocytic MDSCs (G-MDSC) have a $CD11b^+$ Ly-$6G^{hi}$Ly-$6C^{low}$phenotype, whereas monocytic MDSCs (M-MDSC) are usually classified as $CD11b^+$ Ly-$6G^-$ Ly-$6C^{hi}$. In addition, several other surface molecules have been used to identify additional subsets of MDSCs, such as CD80, CD115 (macrophage colony-stimulating factor receptor-M-CSFR) and CD124 (known as IL-4 receptor α-chain or IL-4R) [18].

Interestingly enough, immunosuppressive cells have also been observed in humans, being naturally accumulated in situations of trauma, sepsis, chronic inflammation and tumors [19]. However, the phenotype of human MDSCs is not so clearly defined, in part due to the lack of *gr-1* gene homolog [20]. Human MDSCs are described as myeloid derived cells since they express CD33 and CD11b, specific markers of this cell population, and show negative expression for a combination of molecules used to identify leukocyte lineage, i.e. CD3, CD14, CD19 and CD56 (all of them also known as lineage markers, Lin; [21,22]), together with a low antigen presentation, being HLA-$DR^{-/low}$ [23]. It has been recently described CD15 and CD14 as additional markers for classification of human MDSC subsets in cancer [24]. These two main subpopulations are able to suppress immune function due to arginase-I (Arg-I) activity: while human G-MDSC subset is identified as $CD11b^+/CD14^-/CD15^+$, human M-MDSCs express $CD11b^+/CD14^+$/HLA-$DR^{low/-}$ [25]. Further studies about the phenotype of MDSCs are needed in many other human diseases, including those affecting the CNS.

2.2. Expansion and activation mechanisms of MDSCs

After myelopoiesis has normally occurred, IMCs migrate to peripheral lymphoid organs where they quickly differentiate into mature myeloid cells. In fact, only 2–4% of MDSCs have been observed in the spleen of normal mice. However, as a result of long-term pathological conditions such as chronic inflammation or cancer, MDSCs are able to expand, activate and accumulate as immature cells with the ability to suppress T-cell response [26]. In pathological conditions, the tumor microenvironment releases several factors, such as IL-6, prostaglandins and GM-CSF among others, which promote myelopoiesis and, as a consequence, MDSC expansion [27]. Moreover, diverse molecules trigger their activation and enhance their immunosuppressive function. In this sense, several cytokines such as IFN-γ, IL-4 or IL-13 have demonstrated to play an important role in up-regulating mechanisms involved in the inhibition of the immune response, i.e. increasing the activity of Arg-I and inducible nitric oxide synthase (iNOS) [12,18]. The main signaling pathways involved in the expansion and activation of MDSCs are closely related to the signal transducer and activator of transcription (STAT) family of transcription factors. In fact, STAT3 regulates expansion and survival of MDSCs since it has been described that the inhibition of STAT3 signaling resulted in the abrogation of MDSC expansion [28]. On the other hand, it has been described the involvement of STAT3 in regulating the immunosuppressive function of MDCS [29]. Apart from STAT3, STAT6 and STAT1 are also involved in promoting the activation on these cells [30].

2.3. The suppression of T-cell function

MDSCs are characterized not only by their morphological and phenotypic heterogeneity but also by their ability to impair the immune response. These cells have developed different mechanisms of immunosuppression depending on the subset: whereas G-MDSCs are related to the production of reactive oxygen species (ROS), M-MDSCs exert their immunosuppressive function mainly by increasing the level of nitric oxide (NO; [15]). Together with these mechanisms, other activities of MDSCs related to suppression of T-cell function will be reviewed in this section (Fig. 1).

2.3.1. Alterations in the metabolism of L-Arginine

L-Arginine is the substrate of two enzymes, iNOS (which is able to generate NO and citrulline) and Arg-I (involved in metabolizing L-arginine into urea and L-ornithine within the urea cycle). It has been described that the depletion of this non-essential amino acid from the microenvironment results in the inhibition of T-cell proliferation [31]. The lack of L-arginine is involved in decreasing the expression of CD3 ζ-chain on T-cell, avoiding the up-regulation of cell cycle regulators cyclin D3 and cyclin-dependent kinase 4 [31]. On the other hand, NO production results in abolishing T-cell function mediated by the inhibition of