MDSCs in haematological malignancies

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Myeloid-derived suppressor cells (MDSCs) are a set of immature myeloid lineage cells that include macrophages, granulocytes, and dendritic cell precursors. This subpopulation has been described in relation to the tumour processes at different levels, including resistance to immunotherapy, such as immune checkpoint inhibitors (ICIs). Currently, multiple studies at the preclinical and clinical levels seek to use this cell population for the treatment of different haematological neoplasms, together with ICIs.

Keywords: myeloid-derived suppressor cells (MDSCs) ; immune checkpoint inhibitors (ICIs) ; haematological malignancies ; immune resistance

1. Introduction

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immature myeloid lineage cells that include macrophages, granulocytes, and dendritic cell precursors [1][2]. This cell population has the peculiar ability to suppress both innate and adaptive immune activity [3][4]. The role of these cells is their inhibition of immune cells, mainly T cells, and, to a lesser extent, B and NK cells. In virtually all studies that have been carried out, it has been observed that these cells are associated with a worse response to cancer treatments and lower survival rates in patients with solid and haematological tumours [5][6]. Although most of the studies concerning MDSCs have been carried out in solid tumours, in recent years, the relationship of these cells with haematological malignancies and immune-mediated cytopenias has become more evident [7][8].

This group of cells has also been shown to promote the progression and formation of metastases through remodelling of the tumour microenvironment and angiogenesis through vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and matrix metalloprotease 9 [9][10]. In this way, the presence of MDSCs in the tumour bed is not only a potential biomarker of the aggressiveness, response, and survival of the different tumours (both solid and haematological), it is also a probable therapeutic target in combination with the system's immune checkpoint inhibitors (ICIs) [11][12]. The appearance of ICIs has also marked a milestone in the treatment of different neoplasms, both solid and haematological. Several studies have evaluated the combination of agents directed against MDSCs and immunotherapy as a possible new treatment for different neoplasms.

2. Definition and Role of MDSCs

In the last 5–10 years, a better characterization of MDSCs has been observed in various studies. Likewise, it has been seen that these myeloid cell populations show synergy with different regulatory mechanisms of the immune system, which may be essential in the treatment of different neoplasms. MDSCs are composed of a heterogeneous population of immature myeloid cells (IMCs) in various states of transcriptional activity and differentiation [13]. The myeloid lineage expands clonally under pathological conditions, where increased production of myeloid leukocytes in the bone marrow carries out an important and fundamental defence against bacteria, tumours, or other external agents [14][15].

At the time of induction of the tumour microenvironment (TME), a dysregulation of the immune system occurs that leads to various alterations in the tumour, preventing immune system action [16]. Along with the dysregulation of the immune system, there is also an increase in the expression of inflammatory cytokines. The combinatorial effects of these cytokines can alter myeloid cell differentiation with increased MDSC production, creating an IMC spectrum that is morphologically analogous to granulocytes and monocytes. Through a continuous process of chronic inflammation, different haematologic tumours are also capable of amplifying myelopoiesis, which contributes to the progression and spread of the tumour [17] [18]. MDSCs are attracted to the tumour and its microenvironment through the secretion of different chemotactic substances. Among the different mechanisms that contribute to this process are immunoevasion through the induction of anergy of NK cells [19] and T cells [20], as well as the induction and facilitation of TME processes to promote tumour growth, create and establish a metastatic niche for the spread of cancer, promote angiogenesis, or improve tumour cell

survival through its immunosuppressive activity [21]. From the above, it can be understood that MDSCs actively contribute to the ineffectiveness of the immune system in tumour control and therefore impede the efficacy of immunotherapy against cancer.

3. Classification of MDSCs

MDSCs can be divided into two groups: polymorphonuclear (PMN-MDSC) and monocytic (M-MDSC) [22][23]. In humans, MDSCs are identified by myeloid cell markers CD11b +, CD33 +, HLA-DR low/–, and lineage-specific antigen Lin-negative. In the case of M-MDSC, the target expression is CD11b + CD33 + HLA-DR- / CD14 + CD15-, and for PMN-MDSC, it is CD11b + CD33 + HLA-DR-/CD14-CD15 + [24][25][26]. Despite this classification, in the different tumours, both solid and haematological, it is possible to find the different populations of MDSCs together [27][28]. The different expression markers in the MDSCs are summarized in Table 1 [29][30][31]. M-MDSC and PMN-MDSC have the same expression of CD11b, CD38, CD39, CD40, CD45, CD62L, CD86, CD120, CD162, and PD-L1. It is important to bear in mind that the expression of the different MDSC detection biomarkers may vary depending on the tumour under study.

Table 1. Differential expression markers in the populations of MDSCs in animal models.

MDSC Population	Chemokine Receptor	Cluster of Differentiation *	MHC	Ly6	Mac-2 (Galectin-3)
M-MDSC	CCR2 (high) CCR5 CX3CR1 CXCR1 CXCR2 CXCR4	CD1b CD49d CD54 (high) CD71 CD73	Class I Class II (+/−)	Ly6C + (high)	High
PMN-MDSC	CCR2 CCR5 CX3CR1 CXCR1 CXCR2 CXCR4	CD43 CD54 (low) CD73 (high) CD98 CD244 (+/−)	Class I Class II (+/−)	Ly6C + (low) Ly6G + (high)	Low

Despite the different existing efforts, there is no standardized method that allows the determination of a series of markers to study in the different populations of MDSCs [32], even though, in the future, it will be essential to characterize them in order to bring their in vitro applications to routine clinical practice. The differential expression of MDSC population markers in clinical practice is summarized in Table 2. A number of commonly expressed markers exist between M-MDSCs and PMN-MDSCs: CD13 (low in M-MDSC and high in PMN-MDSC), CD16 (high in M-MDSC and low in PMN-MDSC), CD33 (high in M-MDSC and low in PMN-MDSC), CD34 (high in M-MDSC and low in PMN-MDSC), CD11b, CD38, CD39, CD45, CD62L, CD73, CD115, and CD124.

Table 2. Differential expression markers in the clinical identification of MDSC populations.

Type of MDSC	Chemokine Receptor	Cluster of Differentiation *	HLA-DR	Lin
M-MDSC	CCR2 (high) CXCR4 CXCR1 CXCR2	CD14 (high) CD68 CD80 (+/−) CD83 (+/−) CD86 (+/−) CD163 CD117 (+/−)	Negative	+/− (low)
PMN-MDSC	CCR2 CXCR4 CXCR1 CXCR2	CD15 CD66b CD117	Negative	+/− (low)

4. MDSCs and Haematological Malignancies

In recent years, a multitude of studies have emerged that evaluate the role of MDSCs in haematological malignancies. Most of these studies have associated MDSCs with tumours in more advanced stages, a high tumour burden, and poor treatment results. However, the role of MDSCs must be analysed according to the different haematological neoplasms. In particular, current findings indicate that MDSCs can be considered prognostic markers in haematologic malignancies.

4.1. Lymphoma

The term lymphoma includes both non-Hodgkin's lymphomas (NHL) and Hodgkin's lymphoma (HL). They are clonal diseases of B, T, or NK cells in various stages of differentiation. These cells proliferate in lymph nodes and other lymphoid organs [7][8]. Although treatment strategies have been shown to be effective, a large number of patients may have a relapses of the disease, so new treatment options are being investigated, including therapies that act on the host's immunosuppressive tumour microenvironment (TME) and immune cells, as is the case with checkpoint inhibitors. Patients have been shown to be affected by immunosuppressive cells, such as regulatory T cells (Tregs) and MDSCs, which can counteract the efficacy of these new therapies [14].

4.1.1. MDSCs in Hodgkin's Lymphoma

HL cells are surrounded by a TME, which produces the suppression of the immune response. In a work by Romano et al., subsets of undifferentiated M-MDSC, G-MDSC, and CD34 + MDSC were higher in peripheral blood samples from 60 patients with HL at diagnosis compared to healthy patients. It was also observed that the patients who presented better responses to chemotherapy had lower levels of CD4+ MDSCs. Likewise, CD34+ MDSCs were presented as a promising biomarker for the outcome in HL with a specificity and sensitivity of 92% and 89%, respectively [33].

In another study [34][35], higher levels of CD66b +/CD33dim/HLA-DR-G-MDSC were found in patients with B cell lymphoma at diagnosis, in contrast with healthy controls. A decrease of CD66b + MDSCs from patients' peripheral blood mononuclear cells (PBMCs) increased the levels of proliferating T cells, showing that these MDSCs are immunosuppressive. Poor prognosis and decreased progression-free survival (PFS) were observed in patients with high MDSCs levels.

In one study, three subtypes of MDSCs were reported to be increased in newly diagnosed advanced-stage HL patients, and decreased after at least two cycles of chemotherapy with Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) [36]. However, the immunosuppressive effect and the correlation with the outcome appeared stronger for G-MDSC than for M-MDSC in HL, and only G-MDSC increased in HL patients compared to healthy controls.

4.1.2. MDSCs in Non-Hodgkin's Lymphoma

Lin et al. [37] studied mononuclear cells in 40 patients with B cell NHL and reported that monocytes with a CD14 + HLA-DR low/− profile reduce host immune responsiveness by reducing IFNγ production and suppressing T cell proliferation. According to these reports, NHL patients with a higher number of CD14 + HLA-DR low/− cells had a more advanced stage of the disease.

Analysing various studies of patients with B and T cell NHL, M-MDSCs were found to have higher levels in peripheral blood compared to healthy donors; these elevated levels were correlated with an advanced stage, higher recurrence, higher International Prognostic Index (IPI) score, and lower PFS. M-MDSCs may return to normal after patients achieve remission. Removal of MDSC from patients could re-establish T cell proliferation [38][39][40][41]. G-MDSCs have also been reported to accumulate in patients with HL and B-NHL compared to healthy controls, while reduction of CD66b + cells may re-establish T cell proliferation, similarly to the decrease in M-MDSC [35]. Elevated levels of MDSC, especially M-MDSC, were found in extranodal natural killer (NK)/T cell lymphoma (ENKL) at diagnosis, and these levels were predictors of overall survival. Furthermore, IL-17, ARG1, and iNOS expressions were elevated in ENKL patients, and inhibition of iNOS and ARG1 restored T cell proliferation [42].

In a study applying adoptive NK cell infusion therapy for NHL patients, Bachanova et al. showed that high levels of MDSC are associated with a lack of clinical response, in line with preclinical results that showed that MDSCs mediate NK cell inhibition. In this phase II clinical trial of patients with relapsed or refractory NHL [43], baseline levels of MDSC in peripheral blood were associated with a positive response to haploidentical donor NK cell therapy combined with rituximab (anti-CD20). Interestingly, the non-responders had elevated levels of the T cell immunoreceptor, with immunoglobulin and ITIM (immunoreceptor tyrosine-based inhibition motif) (TIGIT) domains in their T cells. This is consistent with previous work indicating that low TIGIT levels in NK cells confer resistance to MDSC-mediated suppression, and suggests that therapeutic efficacy can be further enhanced by blocking MDSC signalling [44]. In summary, MDSCs, especially M-MDSCs, may participate in carcinogenesis by restraining T cell proliferation in lymphoma.

4.2. Multiple Myeloma

Monoclonal gammopathies are clonal proliferations of B cells in the last maturing stages (plasma cells). They include multiple myeloma (MM), which is a proliferation of neoplastic plasma cells in the bone marrow that are usually associated with typical symptoms (anaemia, bone lesions, kidney failure, hypercalcemia). MM patients usually present increased

levels of immunosuppressive cells and cytokines. In one study, MDSCs levels were increased in patients with MM compared to healthy controls [45]. It was subsequently shown that the levels of M-MDSCs were positively correlated with recurrent MM and negatively with response to treatment [46]. Likewise, it is suggested that G-MDSCs could play a key role in the pathogenesis of MM. G-MDSCs have also been reported to accumulate in both the BM and PB of MM patients compared to healthy controls, leading to higher MM activity and lower PFS [47][48][49][50].

Arg-1, iNOS, ROS, and TNF-α were found to be overexpressed by MDSCs [50]. In a recent report, PMN-MDSCs and their function through increasing Arg-1 are associated with the progression of MM. PMN-MDSC and arginase are raised in MM, and are potential biomarkers of a poor treatment response [51].

Wang et al. [46] and Favarolo et al. [48] studied the immunosuppressive capacities of MDSCs in other immune cells, such as Tregs. Increased levels of Tregs have been found in MM patients compared to controls, as has the induction of Tregs by MDSCs in a cell contact-dependent manner. There are conflicting reports on the effect of the proteasome inhibitor bortezomib and the immunomodulatory agent lenalidomide on MDSCs in the treatment of MM. In various studies [46][52], treatment with bortezomib combined with other drugs, such as dexamethasone or lenalidomide, reduced MDSCs levels in PB.

G-MDSCs can regulate angiogenesis in MM through the expression of P-element Induced Wimpy testis (PIWI)-interacting RNA (piRNA)-823, which promotes DNA methylation; G-MDSCs also increase the carcinogenic potential of MM cells in vitro and in vivo [52][53][54]. It was recently reported that treatment with the demethylating agent decitabine (DAC) inhibited MM cell proliferation in Merwin-11 plasma cell tumour cells (MPC11) and enhanced the immune response of autologous T cells by depleting M-MDSCs. The study demonstrated that MDSC depletion by DAC could decrease MM proliferation, considering that MDSCs are fundamental for MM progression [55]. In their study, Nakamura et al. [56] suggested that IL-18 acts as a key factor for immunosuppression in the MM BM niche through the generation of MDSCs

4.3. Leukaemia

In contrast to the robust body of research addressing lymphoma and MM, studies on MDSC in leukaemia have been relatively limited.

4.3.1. Acute Leukaemias

Several studies reported that MDSCs were accumulated in the PB and BM of patients with acute myeloid leukaemia (AML) in contrast with healthy controls [57], and the therapeutic response of patients with B cell acute lymphoblastic leukaemia (ALL-B) was positively correlated with elevated levels of G-MDSC in both PB and BM [58]. A recent study demonstrated that the V-domain immunoglobulin suppressor of T cell activation (VISTA) immune checkpoint protein is highly expressed in MDSCs in the PB of AML patients. VISTA expression is associated with T cell immunosuppression. Regulation of VISTA by siRNA reduced the ability of MDSCs to inhibit CD8 + T cell activity. Furthermore, a strong positive association was observed between VISTA expression on MDSCs and PD-1 expression on T cells in AML [59].

Using multiplex immunohistochemistry, Hotari et al. [60] found that M1-like macrophages, granzyme B + CD57 + CD8 + T cells, and CD27 + T cells decreased in BM biopsy samples from 52 ALL patients compared to 14 healthy controls, whereas M2-like macrophages and MDSCs increased. Increases in MDSCs and immune markers, such as PD-1 and CTLA-4, have also been associated with immune regulation in ALL [60]. IL-13 secreted by ILC2s in patients with acute promyelocytic leukaemia (APL) increased M-MDSCs levels and amplified tumour development. ILC2-MDSC secretion may be diminished by ATRA treatment [61].

4.3.2. Myeloproliferative Neoplasms

The increasing recognition of MDSCs as markers of a poor prognosis has recently been extended to chronic myeloid leukaemia (CML). Imatinib and dasatinib, which disrupt BCR- and ABL-mediated oncogenic signalling in CML, depleted the levels of MDSCs and their biomarkers IL-10, ARG1, and myeloperoxidase [62]. Furthermore, in high-risk CML patients, levels of ARG1-expressing PD-L1 + MDSCs increased, as did PD-1 expression on T cells, and MDSC levels decreased to normal after therapy with imatinib [63]. In a recent study, TKI therapy decreased the percentage of G-MDSC, but only dasatinib-treated patients experienced a significant reduction in the number of M-MDSCs. Therefore, M-MDSCs were identified as a prognostic factor for dasatinib-treated patients [64]. According to the current literature, MDSC levels in CML are reduced after treatment with TKI and IFN-α interferon in a time- and dose-dependent manner. A reduction in MDSC levels was observed after short-term IFN-α treatment, but MDSC levels increased with long-term therapy. In fact, chronic exposure to low doses of IFN-α may induce a suppressive TME through the activation of MDSCs [65][66][67][68]. This study

showed that the addition of IFN-α to TKI therapy boosts a suppressive TME, with higher levels of Treg, MDSC, and CD4 + PD1 + T cells.

4.3.3. Chronic Lymphocytic Leukaemia (CLL)

In patients with CLL, the levels of M-MDSCs were significantly increased at the time of diagnosis, suppressing T cell activation in vitro and inducing the formation of suppressor regulatory T cells [67]. A separate study included 49 patients with CLL, all of whom had increased levels of M-MDSCs and suppressed CD4 + T cell immune response, which correlates with a worse prognosis [68]. Furthermore, increased levels of M-MDSCs were observed in PB in 50 newly diagnosed CLL patients. Higher levels of M-MDSCs predicted poorer survival rates [69]. In another study, high levels of M-MDSCs predicted failure of chimeric antigen receptor T cell therapy in CLL [70].

4.4. Myelodisplastic Syndromes

Myelodysplastic syndromes (MDSs) are characterized by ineffective dysplastic haematopoiesis associated with aberrant expansion and activation of MDSCs within the bone marrow niche. Increased levels of MDSCs are correlated with a high risk of disease progression and a poor prognosis [65]. In one study, increased expression of PD-1 in haematopoietic stem and progenitor cells and PD-L1 in MDSCs was observed in MDS patients versus healthy donors. High concentrations of S100A9 produced by MDSC in the bone marrow niche of patients with MDS, together with IL-10, TGFβ, and activation of the myelocytomatosis proto-oncogene (MYC), induces PD-L1 formation to facilitate immune evasion [68]. The therapeutic effectiveness of these new agents directed against MDSCs in myelodysplastic syndromes is currently under investigation.

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