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Myeloid-derived suppressor cells in ovarian cancer: friend or foe?

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Abstract

Although previous decades contributed to major progress in targeted therapy of many malignancies, the treatment of gynaecological cancers remains a challenging task. In the evidence of rising cancer mortality, the search for new methods of treatment is a dire need. Exploring the mechanisms of interaction between tumour cells and host immune response may allow the introduction of new, effective therapies – not as toxic and far more efficient than conventional methods of cancer treatment. Epithelial ovarian cancer (EOC) is typically diagnosed at advanced stages. Its incidence and mortality rate is high. Powerful diagnostic tools for this kind of cancer are still under investigation. Multiple mechanisms existing in the ovarian tumour network create a specific immunosuppressive microenvironment, in which accumulation of myeloid-derived suppressor cells (MDSCs) may be a critical component for diagnosis and treatment. This review attempts to verify current knowledge on the role of MDSCs in EOC.

Key words: *ovarian cancer, myeloid-derived suppressor cells (MDSCs), T cells.*

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Introduction

Causes of impaired function of the immune system associated with cancer have been studied for many years, but their final explanation is still ahead of us. The anti-tumour response involves, among others, macrophages, NK cells, and cytotoxic T lymphocytes. Exploring the mechanisms of interaction between tumour cells and host immune response may allow the introduction of new, effective therapies that are not as toxic as conventional methods of cancer treatment. Despite the evidence of anti-tumour responses – including cytotoxic T-lymphocyte response to antigens of the tumour – the host immune system is frequently unable to eliminate the neoplastic clone.

The main mechanisms of tumour escape from host immune system are: changes in the expression of antigens and costimulatory molecules, direct suppression of the function of dendritic cells, T cell cytokine production, and the induction of regulatory T cells (Treg) that have the ability to inhibit the immune response [1, 2]. Tumour microenvironment (TME) may also activate cells other than Treg; over the past few years a new member of the tumour-host interacting cells has been characterized, i.e. suppressor cells derived from myeloid progenitors (myeloid-derived suppressor cells – MDSCs). This population was detected at the end of the 20th century, but its final name was established in 2007 [3]. Previous terms such as immature myeloid cells (IMC) and myeloid suppressor cells (MSC) did not accurately reflect their origin and function. MDSCs are a heterogeneous population of cells derived from myeloid lineage, consisting of immature macrophages, granulocytes, dendritic cells, and other cells in the early stages of differentiation, which are potent immunosuppressants. The presence of MDSCs was established in animal models of cancer as well as in humans [4, 5]. The described cells were initially found in the spleen, bone marrow, and tumour microenvironment and recently – even in the peripheral blood. This population inhibits immune response, including tumour-associated antigens (TAA). The accumulation of these cells also occurs in conditions such as chronic inflammation (including bacterial and parasitic infections), injuries, and graft versus host disease after transplantation of haematopoietic cells [6-9]. In the view of the above, this seems to be a promising approach to block MDSC trafficking and infiltration and therefore reduce suppressive activities of MDSCs in the discussed disorders [10, 11].

Characteristics of myeloid-derived suppressor cells

MDSCs are known as a heterogeneous cell population consisting of myeloid cells in various stages of dif-

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ferentiation without mature myeloid-associate markers on their surface [3, 12]. In murine model tumour, MDSCs were defined as cells with co-expression of CD11b and Gr1 markers; however, a lack of human homologue of Gr1 caused various problems with their immunophenotyping, highlighted in scientific literature [13]. Human MDSCs are less understood but are mostly introduced as immature myeloid cells with surface expression of CD33+ consisting of dendritic cell, macrophage, and granulocyte progenitors [14]. The main function of MDSCs was a generalised suppressive impact on the immune response, predominantly through direct inhibition of the cytotoxic functions of T cells and NK cells [15]. As MDSCs arise from myeloid progenitor cells without the potential of further differentiation into mature dendritic cells, granulocytes, or macrophages, they can be divided into three important phenotypes: granulocytic, promyelocytic, and monocytic [16]. Diversification between monocytic and granulocytic (polymorphonuclear) subsets is based on specific markers ($CD11b^+ Ly6C^{high} Ly6G^-$) typical of monocytes M-MDSCs and different phenotypes ($CD11b^+ Ly6C^{low} Ly6G^+$) common in granulocytes G-MDSCs division [17, 18]. Additionally, this group can express granulocytic marker CD15+ or CD66b+ [19]. There were found also functional differences between each of the subsets: granulocytic MDSCs are able to produce higher levels of arginase and have been shown to generate higher levels of reactive oxygen species (ROS) [20, 21]. This is one of the mechanisms by which granulocytic MDSCs are able to suppress T cells inducing T-cell apoptosis. In addition ROS can block activation of T-cell receptor (TCR) by its nitrosylation, and as a result inhibit binding of an antigen. Monocytic MDSCs can express arginase and inducible nitric oxide synthetase (iNOS); however, they do not produce high levels of ROS [19, 22-25].

MDSCs in tumour microenvironment

Initial studies concerning MDSCs started in the 1990s while on experiments with anti-cancer vaccinations [26]. Further research revealed MDSCs as cells with an exceptional ability to suppress both innate and adaptive immune responses while stimulating tumour angiogenesis, neoplasm invasion, and metastasis [27, 28]. Immature myeloid cells are continually produced in the bone marrow of healthy individuals, and then they differentiate into mature form without causing observable immunosuppression. Normal myeloid cell differentiation is disrupted within cancer environment [29, 30]. Tumour-derived stromal cells are able to release multiple cytokines interfering with the myeloid compartment. A wide range of colony stimulating factors such as GM-CSF, G-CSF, M-CSF, SCF as well as VEGF and IL-3 promote myelopoiesis and partially inhibit myeloid cell maturation [13, 31-34]. Furthermore, pro-inflammatory cytokines – IL-1β, IL-6, and PGE_2 – induce myeloid differentiation towards immunosuppressive MDSCs; IFN-γ along with LPS promotes their multiplying, and then TGF-β impacts on their concentration. Chronic inflammation associated with tumour development is promoted by several mechanisms involved in the production of proangiogenic factors, matrix metalloproteinases (MMPs), and damage-associated molecular pattern molecules (DAMPs). All of the above leads to MDSC accumulation and MDSC suppressive effects [12, 35-39].

Several suppressive mechanisms attributed to MDSCs in tumour environment have been proved so far (Fig. 1). By limiting the amino acids such as L-Arg, L-Trp, and L-Cys, they are able to inhibit T-cell activation as well as proliferation [12, 40]. One of the well-defined mechanisms is upregulation of nitric oxide synthase 2 (NOS2), which generates nitric oxide (NO), ROS, and peroxynitrate. Production of NO (nitric oxide) prevents IL-2 signalling, thereby impairing the proliferation of cytotoxic and memory T cells. Secretion of reactive oxygen species (ROS) inhibits peptide detection by T cells and prompts T-cell apoptosis. The increased peroxynitrate accumulation leads to the nitration of the CD8 TCR with inhibition of CD8+ T-cell activity [41-43]. Downregulation of L-selectin and E-selectin impairs T-cell migration to lymph nodes and the tumour region [44]. Cell-to-cell contact between MDSCs and macrophages as well as cross-talks with dendritic cells (DCs) in tumour-bearing environment promote metastasis and impair anti-tumour function of both cell classes [45]. Also, inhibition of NK function by MDSCs by deactivating NKG2D receptor was revealed. Although MDSCs play an important role in tumour progression, the specific signals triggering the accumulation of MDSCs in cancer patients remain unidentified [46, 47].

Gynaecological oncology and MDSCs

Incidence of breast cancer and female reproductive system neoplasms is continuously increasing [48]. Worldwide, breast and ovarian cancers account for 26.6% (2008) of all cancer cases among females [49]. Breast cancer is the most common cancer among females, with an estimated 249,260 new cases in 2016, while ovarian cancer is responsible for 5% of all oncological deaths and its mortality rate is higher than of any other gynaecological cancer [48, 50, 51]. Among gynaecological cancers, ovarian cancer is the third most frequent, next to *cervix uteri* and *corpus uteri* cancers [48]. Although previous decades contributed to major progress in targeted therapy of many malignancies, the treatment of gynaecological cancers still remains a challenging task [52].

Recent studies have revealed many facts considering gynaecological tumour microenvironment and the critical role of MDSCs in the immune network [53]. Though most studies focus on ovarian cancer, the incidence of MDSCs correlating with abnormal arginase-1 activity has been confirmed so far in endometrial cancer and uterine sarco-

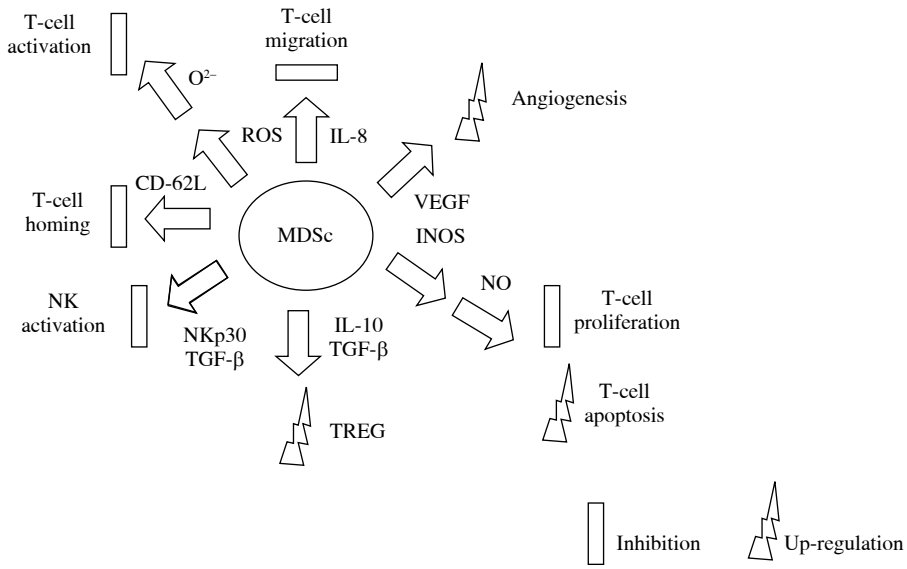

Fig. 1. The role of MDSCs in the suppression of anti-cancer cellular response and tumour growth

ma [54]. In another type of cancer of the female reproductive tract, cervical cancer, the increased accumulation of MDSCs was induced by tumour-derived G-CSF. G-CSF expression was proven to be an independent poor prognostic factor in cervical cancer patients treated with platinum-based chemotherapy. Moreover, MDSC incidence was responsible for the development of cisplatin resistance in G-CSF-producing cervical cancer [55].

MDSC characteristics in ovarian cancer

Epithelial ovarian cancer (EOC) consists of a range of specific histological subtypes. About 70% of cases of EOC are serous carcinoma. Other subtypes are endometrioid, mucinous, and clear cell, which are associated with a worse prognosis than all the other subtypes [56, 57]. A recent study suggests that EOC can be divided into two subtypes based on IL-6, IL-6R, and immune infiltration. The first group comprises tumours with high expression of IL-6R and low infiltration by mature myeloid cells, with good patient survival, suggesting that determination of IL-6R expression might be useful as a prognostic marker. The second group covers tumours without expression of IL-6R, but with a high level of IL-6, and infiltrated with mature CD163+ myeloid cells [58].

EOC is typically diagnosed at advanced stages. The percentage of five-year survival is approx. 20-25% for tumours in clinical stage III according to the International Federation of Gynaecology and Obstetrics (FIGO), and only 5% for stage IV disease, which confirms the great variability in progression-free survival rates and overall survival among patients with advanced EOC [59]. The causes of such a high rate of mortality seem to be related to the complex biology as well as the huge heterogeneity of EOC [60]. Typical treatment – surgical removal of the tumour with additional chemotherapy – is not efficient and leads in the vast majority of cases to progression of the disease [61]. EOC is characterised clinically by ascites and peritoneal implants; molecularly by accumulation of tumour-associated macrophages and MDSCs, which have been suggested since the 1990s as a critical immunosuppressive component in tumour microenvironment [62-64].

Mechanisms guiding MDSCs to human cancer environment

The mechanism inducing MDSCs into TME of EOC is poorly understood. Several studies have suggested a variety of mechanisms of MDSC induction among tumour cell lines, highlighting role of each tumour type's specific combination of inflammatory cytokines. Prostaglandin E_2 (PGE_2) is described specifically for EOC as an inducing factor of CXCR4-CXCL12 axis. It is a possible pathway mediating the attraction of monocytic MDSCs into the TME of ovarian cancer patients. CXCL12, known as stromal cell-derived factor-1, is a well-defined molecule enhancing tumour growth, migration, and metastasis, produced by stromal and tumour cells of TME. CXCL12 and its receptor CXCR4 are greatly involved in cancer progression by direct activation of cancer cells as well as induction of angiogenesis, Treg, and DCs into the tumour surrounding. In peritoneal fluid isolated from EOC patients, both CXCL12 and CXCR4 are controlled by the tumour-associated inflammatory mediator – PGE_2, which attracts MDSCs into the ascites microenvironment. PGE_2 was essential both for expression of functional CXCR4 in can-

cer-associated MDSCs and for production of its ligand CXCL12 [33, 65-67]. In contrast to the above, Lechner *et al*. indicate that the addition of cyclooxygenase 2 (COX2 – the key enzyme in prostaglandin PGE_2 synthesis) inhibitors to ovarian and cervical tumour cell line-PBMC co-cultures did not significantly decrease MDSC induction, which strongly suggests the existence of another mechanism inducing MDSCs in ovarian TME [14]. Interestingly, recent data have revealed that IFN-γ and TNF-α synergise in the induction of COX2 and subsequently hyperactivate MDSCs within the TME of ovarian cancer patients. A new mechanism focuses on the synergistic action of IFN-γ and TNF-α, which could not be achieved by either of these factors alone [68]. IL-6 was the cytokine involved in another possible way of induction of MDSCs in TME of ovarian cancer. IL-6 is a major mediator of cancer-related inflammation, tumour growth, tumour angiogenesis, and tumour myeloid cell infiltration in ovarian cancer. Differentiation of MDSCs can be mediated by IL-6 [3, 12, 15, 58]. Reinartz *et al*. defined a subgroup of ovarian cancer patients with a poor clinical outcome, with high CD163 expression (myeloid cells marker) and high IL-6 levels in ascites [69]. In an experimental study Wouters *et al*. indicate IL-6 and its ligand IL-6R as opposite markers for tumour-infiltrating myeloid cell infiltration and survival. Tumours with a high expression of IL-6R displayed low mature myeloid cell infiltration and a longer disease-specific survival. In contrast, tumours with high epithelial IL-6 expression displayed a dense infiltration of tumour-infiltrating myeloid and were correlated with a shorter survival [58].

MDSCs influence to ovarian cancer progression

Initially MDSCs in ovarian tumour environment were described in 2004 as vascular leukocytes (VLCs); the population of ovarian tumour-associated leukocytes of unknown origin and surface markers such as F4/80 and CD11b [70, 71]. The presence of VLCs highly inhibited CD8+ and CD4+ T-cell activity with IFN-γ release by > 95%. Closer inspection revealed VLC dependence on ARG1 enzyme, and that inhibition with the ARG1-specific inhibitor nor-NOHA restores activation of CD8+ and CD4+ T cells. Additionally, production of ARG-1 results in generation of ROS. The subsequent characterisation of the tumour-associated leukocytes in ovarian cancer provided insight into the phenotype referred to as MDSC [72]. Recently published research has confirmed the "stemness" of MDSCs existing in the ovarian cancer environment. This highlights the importance of interactions between MDSCs and cancer stem cells via the MDSC-microRNA101-CtBP2 network, which may affect the tumour's phenotype and the patient's outcome. MDSCs trigger miRNA101 expression in cancer cells. Therefore, miRNA101 influences the corepressor gene C-terminal binding protein-2 (CtBP2), and CtBP2 directly targeted stem cell core genes resulting in increased cancer cell stemness and increased metastatic and tumorigenic potential [73].

Further studies have implicated the importance of oxidative stress in creating immunosuppressive TME in EOC. Activated monocytes, neutrophils, and MDSCs have started to be considered as the components of the chronic inflammatory environment that suppresses T-cell function. On the one hand, previous studies revealed that ROS generation is one of the main characteristics of MDSCs from tumour-bearing mice, and on the other hand ROS's ability in promoting MDSCs development and/or immunosuppressive activity was mentioned. NADPH oxidase (NOX2), a major source of ROS in activated phagocytes, potentially has multiple effects on the tumour microenvironment that either promotes or inhibits tumour progression, including modulation of the cytokine's influence, inflammatory cell recruitment, and antigen display and cross-presentation [74-77]. However, a recently published experimental study has not indicated NADPH oxidase as a factor of tumour progression in murine EOC. The accumulation of MDSCs locally and systemically was similar in genetically engineered NADPH oxidase-deficient mice in comparison to wild type mice. The suppressive effect of MDSCs on stimulated T-cell proliferation was NADPH oxidase-independent. Although MDSC retention and immunosuppression in murine EOC is NADPH oxidase-independent, the lack of effect of NOX2 on MDSC accumulation and function does not rule out an effect of other sources of ROS [78].

Future therapy

Although new multiple mechanisms of ovarian tumour network are being constantly revealed, a potential target of the immunotherapy is still absent. Recently published studies highlighted that essential components of future therapeutic strategies should include combination treatments aimed at dealing with the complement inhibitors, together with accurate patient selection. Interestingly, the latest achievement regarding future therapy of MDSCs in ovarian cancer is not only targeted therapy [79]. The efficiency of conventional chemotherapy can be increased by using aptamer-A8, which blocks heat shock protein HSP70 on exosomes. This molecule is able to activate MDSCs via two toll-like receptors on their surface. The amount of this molecule is highly increased by chemotherapeutic agents such as cisplatin or 5-fluorouracil, and it is correlated with higher activation of MDSCs. This mechanism was not observed if chemotherapeutics were combined with A8, which strongly potentiated the antitumor effect of the drugs [80]. Another interesting feature of TME in EOC is correlation between Th17 and MDSC-associated NOS2 and MDSC-produced exogenous NO. The development of human Th17 cells from naive, effector, and memory CD4+ T-cell precursors is induced by the previously identified Th17-driving cytokines (IL-1β,

IL-6, and IL-23) or by IL-1β/IL-6/IL-23-producing MDSCs. Th17 increase is promoted by NO produced by human MDSCs and mainly depends on the induction of endogenous NOS2 in differentiating CD4+ T cells [81-83].

The authors declare no conflict of interest.

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