

Myeloid derived suppressor cells in breast cancer: A novel therapeutic target?

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Author contributions: Weston RM researched the field, extracted and compiled the findings; Stover CM discussed the evaluation and revised the paper.

Conflict-of-interest statement: The authors declare no conflict of interest related to this publication.

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Manuscript source: Invited manuscript

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Received: August 26, 2016

Peer-review started: August 29, 2016

First decision: September 27, 2016

Revised: October 16, 2016

Accepted: October 25, 2016

Article in press: October 27, 2016

Published online: November 27, 2016

Abstract

The relationship of the immune system and tumour cells is complex; although recognised that the immune system can protect the host against tumour development, the immune system also facilitates tumour progression through immune suppression. Pro-inflammatory mediators associated with chronic inflammation are responsible for the expansion and activation of myeloid derived suppressor cells (MDSCs); a heterogeneous group of cells that originates from myeloid progenitor cells but does not complete the final stages of differentiation. A causal relationship between chronic inflammation and tumour progression relies on the accumulation and maintenance of MDSCs as its linchpin; responsible for immunosuppression through the down-regulation of anti-tumour responses. MDSCs cause immunosuppression through a number of mechanisms; inhibiting the proliferation of CD4⁺ and CD8⁺ T cells, blocking natural killer cell activation and limiting dendritic cell maturation and function. As well as using various mechanisms to inhibit adaptive and immune responses, MDSCs also have non-immunological functions that aid tumour spread; including directly promoting tumour proliferation and metastasis by having an important role in tumour angiogenesis, secretion of matrix metalloproteinases and induction of epithelial-mesenchymal transition. Breast cancer is the most common cancer among women in the United Kingdom with 44540 new cases of invasive carcinoma in 2013 and results in the second highest cancer mortality rate in women, with 11600 deaths in 2012. Considering this, the need for novel therapeutic interventions is higher than ever. This review summarises the rationale for the targeting of MDSCs in breast cancer as a realistic avenue to increase survival from breast cancer.

Key words: Breast cancer; Immune cells; Treatment; Suppression; Survival

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Core tip: Breast cancer is the most common cancer among women in the United Kingdom; there were 44540 new cases of invasive carcinoma in 2013. The incidence rate is 169.8:100000, an increase of 5.5% in 10 years. Despite significant advances in the detection and treatment of breast cancer, breast cancer still results in 11600 deaths a year; the second highest number of cancer deaths in women. With increased appreciation of the sustaining importance of cells in the tumour microenvironment, in particular myeloid derived suppressor cells, their targeting is being considered as a novel treatment approach.

Weston RM, Stover CM. Myeloid derived suppressor cells in breast cancer: A novel therapeutic target? *World J Immunol* 2015; 6(3): 119-125 Available from: URL: <http://www.wjgnet.com/2219-2824/full/v6/i3/119.htm> DOI: <http://dx.doi.org/10.5411/wji.v6.i3.119>

INTRODUCTION

Breast cancer is the most common cancer among women in the United Kingdom; there were 44540 new cases of invasive carcinoma in 2013. The incidence rate is 169.8:100000, an increase of 5.5% in 10 years^[1]. Despite significant advances in the detection and treatment of breast cancer, breast cancer still results in 11600 deaths a year; the second highest number of cancer deaths in women^[2,3]. With increased appreciation of the sustaining importance of cells in the tumour microenvironment, in particular myeloid derived suppressor cells, their targeting is being considered as a novel treatment approach.

Myeloid derived suppressor cells (MDSCs) originate from myeloid progenitor cells in the bone marrow but do not complete the final stages of differentiation. They are immune modulatory cells which expand in cancer and go on to block tumour immunity and facilitate tumour progression^[4]. MDSCs can be identified by surface markers and their functional ability to suppress the immune system^[5,6], with the surface marker expression on human MDSCs being CD33⁺CD11b⁺HLA-DR^{low/neg}. The cells can also be identified through the absence of markers that would usually be found on mature lymphoid and myeloid cells^[7,8]. Due to different factors involved in cell development and activation, the expression of surface markers is not limited to those mentioned above; there is a large diversity in MDSCs found in different cancers (CD11b⁺CD33⁺ in non small cell lung carcinoma; CD11b⁺CD33⁺LIN⁻HLA-DR⁻ in Colon, breast, renal, lung, pancreatic, gastric and oesophageal carcinoma; CD11b⁺CD14⁺CD15⁻ in melanoma; CD11b⁺CD33⁺CD14⁺ in head and neck squamous cell carcinoma^[8,9]). This is because the factors of stimulation originate from the tumour cells themselves and a particular phenotype of MDSCs is produced that depends on the inducer molecules released from the tumour^[6]. Therefore, despite

MDSCs having recognisable surface markers, most of these are not unique and the most effective way to identify MDSCs is by their immunosuppressive function^[8].

INFLAMMATION, MDSCS AND CANCER

Chronic inflammation is linked to an increased risk of cancer, with experiments showing that high levels of pro-inflammatory mediators cause an increase in tumour development^[10-12]. There are several mechanisms for this; induction of cell proliferation, increased angiogenesis, triggering of genetic changes and expansion and activation of MDSCs^[4,5,10]. Inflammation-associated molecules, such as vascular endothelial growth factor (VEGF) and granulocyte macrophage colony-stimulating factor (GM-CSF), have been associated with the accumulation of MDSCs^[11] and pro-inflammatory cytokines have been linked to MDSC induction^[10]. These findings indicate that the link between inflammation and cancer is the induction of MDSCs and their inhibition of tumour immunity. Bunt *et al.*^[10] developed a causal relationship between chronic inflammation and tumour progression: Proliferation of tumour cells induces an inflammatory microenvironment consisting of pro-inflammatory factors, causing induction, accumulation and maintenance of MDSCs which leads to immune suppression; facilitating the survival and proliferation of the tumour cells. As well as inflammatory mediators being involved in the activation of MDSCs, MDSCs themselves produce pro-inflammatory factors. These factors, for example S100A8, S100A9 and interleukin (IL)-6, maintain the inflammatory environment and in turn maintain the MDSC population^[6].

UPREGULATION OF MDSCS

MDSCs are up-regulated by a variety of pro-inflammatory mediators, including S100A8/S100A9, IL-1 β , IL-6 and prostaglandin E₂ (PGE₂); leading to immune suppression and proliferation of malignant cells.

S100A8 and S100A9, members of the S100 family of calcium binding proteins, act as inflammatory mediators. Elevated levels of these proteins in serum indicate inflammation and/or recurrent infection with up-regulation found in many cancer patients^[4], leading to the hypothesis that S100A8/9 contribute to the recruitment of MDSCs. Not only do MDSCs have receptors for S100A8/9 but also have an ability to synthesise and secrete these proteins, allowing a positive feedback loop to ensure maintenance of the MDSC population^[4]. When the binding of S100A8/9 was blocked, there was a reduction in MDSC accumulation indicating that these pro-inflammatory mediators are indeed involved in the accumulation of MDSCs^[4]. When tissue sections from 101 invasive ductal carcinoma cases were studied, co-expression of the two S100 proteins was associated with poor tumour differentiation, vessel invasion and node metastasis, indicating that in invasive ductal carcinoma, over-expression of the S100A8/A9 complexes was

associated with poor prognosis^[12].

IL-1 β is important in mediating inflammatory responses, enhancing the accumulation of MDSCs and promoting tumour progression. When the IL-1 receptor is knocked out in murine models, there is a delay in MDSC accumulation and reduced tumour progression, indicating the importance of the interaction between IL-1 β (inflammation) and MDSCs^[10,13]. When IL-1 receptor knock-out mice were inoculated with IL-6-producing tumour cells, there was partial restoration of MDSC accumulation and tumour progression, indicating that IL-6 has a role as a downstream mediator of this IL-1 β -induced process^[13]. The stimulation of a variety of cell types by IL-1 β leads to an increased production of PGE₂, VEGF and GM-CSF; molecules all associated with the induction of MDSCs. As MDSCs do not have a receptor for IL-1 β , it is therefore likely that these molecules could therefore be the downstream mechanism for IL-1 β -induced immune suppression^[10].

IMMUNE SUPPRESSIVE ACTIVITIES OF MDSCS

MDSCs play an important role in tumour progression through the down-regulation of anti-tumour responses. As the tumour develops, the accumulation of MDSCs in the blood and lymphoid tissue is increased with patients newly diagnosed with breast cancer having double the number of circulating MDSCs compared to healthy volunteers^[14]. There is a correlation between increasing levels of circulating MDSCs, clinical stage of breast cancer and decreased survival rate; the highest level of MDSCs are found in those with metastatic disease, stage IV^[14]. MDSCs cause suppression through a number of mechanisms; inhibiting the proliferation of CD4⁺ and CD8⁺ T cells, blocking natural killer cell activation, limiting dendritic cell (DC) maturation and function and impacting on antigen presentation^[4,7,13].

Inhibition of T cell-mediated anti-tumour immunity - biochemical switches

The presence of MDSCs in cancer patients strongly correlates with the absence of antigen-specific T cells, explaining the immunosuppression seen in sufferers^[15,16]. Inhibition of T cell-mediated anti-tumour immunity is due to the production of arginase, reactive oxygen species (ROS), inducible nitric oxide synthase (iNOS), IL-10 and by isolating cystine and limiting availability of cysteine^[17].

The cell's requirement for the essential amino acid cysteine is increased during proliferation, differentiation and activation by an antigen. Cells usually synthesise this cysteine by the enzyme cystathionase, converting intracellular methionine to cysteine. Cells are also able to reduce cystine to cysteine in the cytoplasm after being imported *via* the Xc⁻ cystine/glutamate antiporter^[9,17]. T cells lack both cystathionase and a functional antiporter, therefore depend on antigen presenting cells (APCs) to provide cysteine which is exported *via* the ASC neutral amino acid transporter. APCs also release thioredoxin,

an enzyme that reduces extracellular cystine to cysteine which can then be taken up directly by T cells. MDSCs also express the antiporter and are able to import cystine, competing with APCs for extracellular cystine. Since MDSCs do not express the ASC transporter and are therefore unable to export cysteine, there is a reduced amount of exported cysteine available to be taken up by T cells. As the MDSC burden increases, there is less cystine available for APCs and less cysteine available for T cells to import. MDSCs also disrupt the function of thioredoxin. As a consequence, T cells are deprived of the essential cysteine required for activation and function^[9,17].

PGE₂ produced by tumour cells can induce up-regulation of arginase 1 in MDSCs, leading to increased consumption and reduced availability of arginine, an amino acid required by T cells for protein synthesis^[9]. This depletion of arginine impairs T cell signal transduction and function due to loss of T cell receptor signalling and the inhibition of the cell cycle in G₀ phase^[18]. A significant increase in arginase levels has been found in patients with renal cell carcinoma compared to controls, resulting in a decrease in arginine levels. By using specific inhibitors to block arginase activity, suppression is removed and allows development of an effective anti-tumour response^[18].

Indoleamine 2, 3 dioxygenase (IDO) is an enzyme that is responsible for the break-down of tryptophan, an essential amino acid for protein synthesis. Expression of IDO by MDSCs inhibits T cell proliferation and induces T cell apoptosis through depletion of tryptophan and production of cytotoxic metabolites^[9]. IDO expression was increased in MDSCs isolated from resected invasive ductal carcinoma tissue. This up-regulation requires phosphorylation of signal transducer and activator of transcription 3 (STAT3); increased levels of STAT3 phosphorylation is found in MDSCs. When an IDO inhibitor, 1-methyl-L-tryptophan, or a STAT3 antagonist was used, the MDSCs immunosuppressive activity on T cells was blocked, indicating that STAT3-dependent IDO expression mediates the immunosuppressive effects of MDSCs in breast cancer^[19]. IDO has also been found to accumulate in tumour-infiltrating DCs, further suppressing T cell activity^[3].

iNOS, an enzyme expressed in MDSCs, catalyses the reaction between L-arginine and oxygen to produce L-citrulline and nitric oxide (NO); NO can lead to T cell inhibition through various mechanisms. NO activates cyclic guanosine monophosphate-dependent protein kinase, leading to inhibition of IL-2 receptor signalling and in turn preventing activation of T cells. NO is also able to accelerate tumour growth and may lead to T cell apoptosis^[9,18].

As L-arginine is depleted by MDSCs, iNOS switches to production of O₂⁻, a superoxide anion which goes on to react with other molecules to form ROS and reactive nitrogen species, such as peroxynitrite. Peroxynitrite, which is produced when O₂⁻ reacts with NO, is able to diffuse through the cell membrane, acting as an

intracellular messenger and altering protein functions through nitration of amino acid residues. This strong oxidising agent has the ability to inhibit cytotoxic T cell responses by catalysing the nitration of the T cell receptor and in turn, preventing T cell-peptide-major histocompatibility complex interactions^[9,20]. Peroxynitrite also induces T cell apoptosis through the inhibition of phosphorylation events in the T cell signal transduction pathway^[9].

Hydrogen peroxide is formed from the ROS O_2^- and H^+ and has similar effects as peroxynitrite, impairing T cell receptor signalling, and also inducing T cell apoptosis by increasing the expression of CD95, a death receptor^[9].

Limiting DC function

DCs, as part of the innate immune system are the most important APCs for activation of naïve T cells. Since DCs are derived from the myeloid lineage, DC defects in cancer are likely due to abnormal or incomplete differentiation of DCs due to tumour-derived factors. The abnormal differentiation results in decreased production of mature DCs, accumulation of immature DCs that cannot produce cytokines, and increased production of MDSCs^[21]. The reduction in number of mature DCs is closely associated with an accumulation of MDSCs^[11,21]. Although immature DCs can process and present antigen, there are no co-stimulatory molecules. This fact, as well as a lack of stimulatory cytokines, may result in T cell tolerance^[21]. In cancer, MDSCs inhibit DC production of IL-12 by producing IL-10, decreasing T cell activation and leading to immune suppression and tumour development^[22].

MDSCS AS THERAPEUTIC TARGET

Apart from their immune suppressive function, MDSCs directly promote tumour proliferation and metastasis by furthering tumour angiogenesis^[4,7,23]. Tumour blood vessels are important for providing the blood supply required for the development of the tumour, its progression and metastasis. When tumours are injected with MDSCs, there is increased blood vessel growth and maturation^[24]. MDSCs are also able to incorporate themselves into the tumour endothelium, acquiring endothelial cell properties; expressing endothelial cell markers and leading to tumour vascularisation^[24,25]. Immunotherapies need to overcome the break MDSCs exert on the host's immune responses^[6,26]. Studies have shown that a reduction in the immunosuppressive function of MDSCs is required for the induction of anti-breast immune responses^[27], demonstrating that targeting MDSCs will increase effectiveness of immunotherapies.

Markowitz *et al.*^[26] reviewed studies to determine that there are four main ways that the immunosuppressive effects of MDSCs can be reversed: Forcing MDSCs to differentiate into more mature states; inhibiting expansion of MDSCs accumulating at tumour sites and blocking the function of MDSCs.

Forced MDSC differentiation

Treatment of cancer patients with all-trans retinoic acid (ATRA) resulted in a substantial decrease in the number of MDSCs and an improvement in immune responses without significant toxicity^[28]. ATRA delivers these results through differentiation of MDSCs to mature myeloid cells through inhibition of ROS production; ATRA acts to upregulate glutathione synthase, leading to an accumulation of glutathione^[29]. By determining the mechanism of action and the concentration of ATRA required for a response, there is potential for a therapeutic agent that could be tested further, perhaps in combination with cancer vaccines.

Inhibiting MDSC expansion

Therapeutics that prevent MDSC expansion include STAT3 inhibitors, tyrosine kinase inhibitors and amino-bisphosphonates. Cytotoxic agents such as gemcitabine, 5-FU and cisplatin may directly decrease MDSC accumulation^[26,30].

Inhibiting receptor tyrosine kinases: Sunitinib, an inhibitor of receptor tyrosine kinases involved in breast cancer growth and metastasis which bind VEGF and platelet-derived growth factor, reduces elevated levels of MDSCs in cancer patients^[31,32]. Preclinical studies using a breast cancer model showed that sunitinib, in combination with docetaxel, enhanced the anti-tumour activity of the alkaloid docetaxel and increased survival. In a phase II trial, sunitinib in combination with docetaxel, showed promising anti-tumour activity in patients suffering from advanced breast cancer without significant drug-drug interactions^[31].

In light of these results, Bergh *et al.*^[31] carried out a prospective, multicentre, randomised phase III trial designed to determine if progression-free survival was prolonged when patients were treated with sunitinib and docetaxel rather than docetaxel alone. Progression-free survival is the time that passes from the first day of treatment and the date on which the disease progresses. The results of this study contrasted those expected; despite improving the objective response rate, the treatment failed to prolong the progression-free survival^[31]. Objective response rate is the percentage of patients whose cancer shrinks or disappears after treatment.

Although this treatment regime is not recommended for clinical use, it does not rule out the possibility of using tyrosine kinase inhibitors to target MDSCs in breast cancer.

Inhibiting matrix metalloproteinase-9: MDSC expansion can also be acted against by inhibiting matrix metalloproteinase-9 (MMP-9); an enzyme secreted in high levels by MDSCs that is capable of breaking down extracellular matrix components and is responsible for tumour metastasis promotion and tumour vascularisation^[9]. Although MMP inhibitors have either

failed or showed toxicity when studied as a therapeutic intervention in clinical trials^[33], it has been discovered that amino-bisphosphonates have the ability to inhibit MMP-9; leading to impaired VEGF availability and therefore a reduction in tumour angiogenesis^[34]. Zoledronic acid is a potent amino-bisphosphonate that was developed to treat bony metastases in cancer patients; it also targets MDSCs by preventing the differentiation of immature myeloid cells into MDSCs and has been found to prolong disease-free survival in breast cancer patients when used as an adjuvant in combination therapy^[35-37]. In models of pancreatic cancer, zoledronic acid was effective in impairing intra-tumoural MDSC accumulation and depleting MDSCs, resulting in delayed tumour growth and an increased immune response. There was an increased recruitment of T cells to the tumour, showing that treatment with zoledronic acid improved the anti-tumour response. The mechanism of action is unclear for both of these effects, however, meaning that further work is required^[38]. The efficacy of a direct antitumour effect of bisphosphonates may be enhanced by the adjuvant administration of an anion transport blocker^[39].

Blocked function of MDSCs

Reactive oxygen species: ROS prevent T cell signalling through nitration of the T cell receptor. Breast tumours are sensitive to oxidative stress, typically expressing higher levels of ROS than normal cells due to increased intracellular ROS production, leading to dysregulation in the redox balance^[40]. Kusmartsev *et al.*^[41] demonstrated that *ex vivo* neutralisation of ROS in immature myeloid cells derived from spleens of tumour bearing mice led to differentiation of cells away from their MDSC to a macrophage phenotype. Therefore, inhibitors of free radical formation may be useful in the treatment of breast cancer.

NOV-002, a glutathione disulphide imitator, induces S-glutathionylation, the post-translational modification of cysteine residues through the addition of glutathione. This leads to inhibition of free radical formation^[40]. Drugs targeting S-glutathionylation effect cell signalling pathways, inhibit DNA repair, have inhibitory effects on tumour cell invasion, proliferation and survival^[40,42].

Since chemotherapy is generally less effective in HER-2 negative breast cancer, Montero *et al.*^[40] hypothesised that the addition of NOV-002, to inhibit ROS, to a standard chemotherapy programme would increase response rates to chemotherapy compared to if the patient was just being treated with chemotherapy alone. To test this hypothesis, thirty-nine women with newly diagnosed stage II-IIIc HER-2 negative breast cancer were enrolled in a clinical trial and received doxorubicin and cyclophosphamide, followed by docetaxel every three weeks, in conjunction with daily doses of NOV-002. Fifteen of the patients achieved a pathologic complete response (pCR) rate, a higher response than would be expected from chemotherapy alone. It was also found that patients who had lower levels of circulating MDSCs at their last cycle of chemotherapy had a significantly

higher likelihood of a pCR^[40]. However, since the study was of small size with no randomised control, addition of NOV-002 cannot be conclusively identified as a causal factor for the higher pCR rates. To determine this and if circulating MDSCs can be used to predict patient response, a much larger, randomised control trial needs to be carried out.

IL-12: IL-12 can override the activity of immune suppressing cells and promote anti-tumour responses, giving it the potential to be used as a therapeutic agent by modulating MDSC activity. IL-12 is the major cytokine responsible for the differentiation of T helper cells to promote cell-mediated immunity and also stimulates the proliferation of activated T cells^[43].

MDSCs decrease IL-12 production. When treating MDSCs with IL-12 *in vitro* and *ex vivo*, up-regulation of co-stimulatory molecules CD80 and CD86 on MDSCs was noted, indicating a change in cell phenotype with a new potential for the cells to activate T cells rather than suppress them. There was decreased percentage of MDSCs in the tumour microenvironment and an increased percentage of cytotoxic T cells of CD45⁺ hematopoietic cells. As a result of these benefits, IL-12 treatment resulted in an increase in overall survival and a reduction in metastasis in a mouse model of breast cancer^[43]. These findings identify IL-12 as having significant potential as a therapeutic agent in metastatic breast cancer with the benefit of being a single-cytokine based therapy that could work alone as well as in combination with another agent^[43].

Cysteine as chemo-preventative therapy

High levels of cysteine correlate with reduced breast cancer risk. There may be potential in cysteine or its derivatives as a chemo-preventative therapy against breast cancer to help to biochemically redress the balance of T cell vs MDSC activities. Although cysteine is commercially available as a dietary supplement, neural toxicity was observed in mice with high doses, meaning that cysteine may not be ideal for therapeutic use^[44]. N-acetylcysteine is a synthetic precursor of cysteine and glutathione and is already used as a mucolytic agent in humans, appearing safe even in high doses^[45]. It has been shown in rat models to be a promising candidate for cancer chemo-prevention^[46].

CONCLUSION

MDSCs play a crucial role in tumour progression, responsible for immunosuppression of the host's immune system *via* a multitude of mechanisms. The literature shows MDSCs have a significant role in the development and spread of cancer but it should be noted that research into the action of MDSCs specifically in breast cancer is limited, with most knowledge gained from murine models. Although useful, this knowledge has its limitations as murine responses cannot be assumed to correspond directly with human responses. Much

of the knowledge of MDSCs in human cancers comes from studies on renal cell carcinoma and colon cancer^[49]; again, whilst useful, MDSCs in breast cancer will differ in terms of surface markers and therefore may act slightly differently. Further clinical studies involving breast cancer patients need to be done to determine the true significance of the role that MDSCs have.

Since the level of circulating levels of MDSCs is a strong prognostic indicator^[47], incorporating some of these features into the traditional TNM classification and staging for breast cancers may be helpful in determining the scope of the patient's illness, prognosis and the most effective treatment options on a personalised basis.

Despite there being several potential mechanisms to target MDSCs, there are currently no established therapies to target these mechanisms; the heterogeneity of MDSCs remains a hurdle for MDSC targeted treatments. The lack of unique markers and limited analysis of tumour associated cells hampers progress in the field^[48]. It is exciting to consider MDSC targeted treatments for incorporation in therapeutic regimes of breast cancer, which could further involve immune checkpoint blockade inhibition or breast cancer vaccines^[49]. A significant technological advance in *ex vivo* differentiation of tumour specific MDSC has recently been made^[50].

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P- Reviewer: Vetvicka V, Wang L **S- Editor:** Kong JX **L- Editor:** A
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