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Bone Marrow Stromal Cells As Immunomodulators. A Primer For Dermatologists

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Abstract

Bone marrow stromal cells (BMSCs, also known as mesenchymal stem cells or MSCs) represent a unique cell population in the bone marrow with a long-known function to support hematopoiesis and replace skeletal tissues. The recent discovery that BMSCs also possess potent immunoregulatory features attracted a great deal of attention from stem cell biologists, immunologists and clinicians of different specialties worldwide. Initial clinical experience along with several animal models suggested that intravenously delivered BMSCs are able to regulate a wide variety of host immune cells and act in a way that is beneficial for the recipient in a variety of diseases. The role of the present review is to give a short introduction to the biology of BMSCs and to summarize our current understanding of how BMSCs modulate the immune system with special emphasis on available clinical data. Considering the audience of this journal we will also attempt to guide dermatologists in choosing the right skin conditions where BMSCs might be considered as a therapeutic alternative.

Introduction

Interestingly, bone marrow stromal cells or BMSCs (more commonly called Mesenchymal Stem Cells or MSCs) have been in clinical use for graft vs. host disease (GVHD) before much of their basic biology was known. The use of BMSCs to treat immunologic conditions has opened up a whole new area of cellular therapy in medicine. In order to understand how BMSCs act in various disease settings we have to consider the different cell populations residing in the bone marrow surrounding the BMSCs, their connections and understand the often-confusing terminology used in the literature describing these cells.

The most important role of the bone marrow in postnatal life is to replenish blood cells, a job performed by self-renewing hematopoietic stem cells (HSCs). HSCs give rise to all blood lineages following a multistep differentiation process¹. In order for HSCs to retain their stem cell properties they need to reside in a special microenvironment (referred to as

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stem cell niche) that provides nutrients, growth factors, and other supporting elements. This niche must also protect the HSCs from harm such as circulating toxins, pathogens or activated pro-inflammatory cells. These “nursing” functions are supplied by the bone marrow stromal cells, or BMSCs in short². BMSCs, in fact represent a mixed cell population composed of multipotent skeletal stem cells, transient amplifying skeletal progenitors, and bone marrow stromal fibroblasts. In the bone marrow cavity skeletal progenitors are responsible for building the 3 dimensional skeletal structure that serves as the hematopoietic niche, by differentiating into osteoblasts, chondroblasts, adipocytes, and stromal fibroblasts. When skeletal progenitors are isolated and cultured *in vitro* they give rise to transient amplifying cells, and mature stromal fibroblasts. Upon addition of appropriate differentiation cocktails to the cell culture, the skeletal stem cells can be differentiated into osteoblasts, chondroblasts, and adipocytes. If no factors are added, however, the isolated cells will remain a mixture of skeletal stem cells, stromal fibroblasts, and proliferating skeletal progenitors - and no more than 10% of this mixture is likely to satisfy the criteria to be stem cells. With time, the number of actual stem cells will decrease, and the culture will slowly lose its multipotency, although the cells can still be propagated³.

Due to the fact that there is no known single phenotypic marker exclusively expressed by BMSCs, their isolation from the bone marrow, or identification in *in vitro* cultures is based on negative selection and a combination of a variety of markers. BMSCs are void of hematopoietic and endothelial markers, hence they should stain negative for CD45, CD34, all hematopoietic lineage markers, and CD31. Surface markers that are used to characterize MSCs include CD29, CD73, CD90, CD105, and CD106 (both mouse and human), STRO-1 (human), and CD146, which is a marker only found in human neural crest origin of retinal and choroidal pericytes, and skeletal stem cells, but not their progenies⁴ (Fig 1.)

Nomenclature

Since BMSCs represent a mixed population of adult stem cells and their mature derivatives, and they are also not mesenchymal in origin it is imprecise to call them Mesenchymal Stem Cells or MSCs. Currently, there are more than 20 terms (summarized in Table 1) used to describe the same plastic adherent bone marrow derived population. The most common name in use is MSCs, followed by the more correct bone marrow stromal cell (BMSC). Other names include mesenchymal stromal cells, bone marrow stromal stem cells, mesenchymal progenitor cells, or multipotent stromal cells⁵. Regardless of how these cells are referred to in the literature, one must rely on their isolation, plastic adherence, culture characteristics and phenotypic markers to define them as BMSCs.

Sources of stromal cells

Although the majority of published studies use the bone marrow as the primary source of cultured stromal cells from both mice and the human body, in humans, cord blood, amniotic membrane, spleen, thymus, liver, adipose tissue or gingival tissue derived “mesenchymal stem cells” have also been studied, and found to have similar immunomodulatory properties⁶. In the bone marrow, the skeletal stem cells seem to reside in the perivascular space directly adjacent to endothelial cells, and can be defined as pericytes⁴. It is likely that

tissue-specific stem cells in different organs all reside in the perivascular space of the tissue's microvasculature and upon isolation they give rise to tissue specific stem cells, transient amplifying progenitor cells and organ specific stromal fibroblasts just like BMSCs do. After receiving appropriate differentiation signals, however, tissue specific stem cells can differentiate into their organ specific mature cell phenotype (hepatocyte when isolated from the liver, amniotic membrane when derived from the placenta etc.) and possibly also into mature cells of other tissues (a phenomenon called plasticity)³. Interestingly, many groups have also demonstrated immune-suppressive potential of dermal fibroblasts, a cell population free of stem cell characteristics^{7,8}. Although this observation is still controversial it raises the question if stemness is really necessary for immunosuppression or stem cells merely give rise to the immune-modulating stromal fibroblast pool.

Syngeneic versus allogeneic BMSCs

BMSCs possess immune-modulatory properties in syngeneic, allogeneic and even xenogeneic settings. In murine models this means that cells cultured from different strains (or even different species) are as effective as cells grown from the same strain. If we induce a certain pathology in a C57/B6 mouse strain and use BMSCs from syngeneic C57/B6 mice⁹, allogeneic Balb/C animals¹⁰ or even humans¹¹, the injected cells will have comparable therapeutic efficacy.

From a clinical standpoint this means that if we wish to use BMSCs to treat a patient suffering from an inflammatory condition we can either culture the patient's own BMSCs or use allogeneic (banked) BMSCs - derived from healthy volunteers. Clearly, the latter method is a convenient and predictable way of administering BMSCs and in urgent settings might be the only feasible solution. On the other hand growing and re-infusing the patient's own cells is always preferred in order to avoid the extra risk of transferring undetected pathogens from the donors, but this can not be used in an emergency situations.

Immunogenicity of BMSCs

One surprising feature of BMSCs is that when injected they do not mount an immune reaction even if they are from a third party. It seems plausible that the wide array of immunosuppressive factors secreted by BMSCs together with the low expression of MHC molecules (MHC II is virtually absent)¹² render these cells tolerant to rejection. Although NK cells should attack BMSCs due to their low expression of MHC class I molecules, it has been shown that BMSCs are equipped with several mechanisms that protects them for NK induced lysis. Among these mechanisms IDO and PGE2 release is thought to play a major role^{13,14}. Although some reports support the hypothesis that BMSCs are immune-privileged¹⁵ many others demonstrate induction of the adaptive immunity along with generation of BMSC specific memory T cells¹⁶. The issue whether BMSCs are immunogenic, however, is somewhat pragmatic. Most researchers agree that the vast majority of BMSCs (autologous or allogeneic) disappear in a relatively short amount of time (2–4 days on average) after being infused into the host¹⁷. Their presence is temporary and they are capable of reprogramming immune cells within this narrow time frame, affecting disease pathology long after they become undetectable. This - combined with the fact that

both syngeneic and allogeneic cells have similar immune suppressive properties^{18–20} – makes it irrelevant if BMSCs disappear due to spontaneous apoptosis, or as a result of immune mediated attack.

BMSCs and the immune system

The first clinical report calling attention to BMSCs came from LeBlanc et al. in 2004 describing a case of acute GVHD where cultured, third party, intravenously delivered BMSCs reversed the therapy resistant disease process²¹. Acute GVHD is a result of the uncontrolled attack of donor T lymphocytes against host tissues. The idea to infuse cultured stromal cells was based on observations that BMSCs suppress the proliferation of T cells in in vitro lymphocyte co-culture systems²² as well as in a primate skin transplantation model²³.

Following this report numerous laboratories started to explore the molecular basis of the immune-suppression. As a result of numerous studies we now know that BMSCs in fact play a role in all aspects of the immune response²². In addition to the original observations on T cells BMSCs can also suppress dendritic cell differentiation and maturation as well as Th1, Th2 and Th17 and cytotoxic lymphocyte functions, while inducing the differentiation of regulatory T cells (Treg). These effects together can impair antigen presentation and the guidance of B-cells and cytotoxic T lymphocytes by helper T cells. Although the direct effect on B lymphocytes is somewhat controversial based on in vitro data, in a mouse model of ragweed induced asthma we have demonstrated that BMSC treatment significantly decreases total IgG1 and IgE levels¹⁰. Rafei et al. also suggested that BMSCs suppress IgG production through inducing PAX5²⁴. In addition, it is likely that concurrent suppression of helper T cells *in vivo* will also impair B cell specific functions.²⁴ BMSCs also facilitate the production of immunosuppressive monocyte/macrophages designated as M2 cells^{19,25}. As a result, in vivo effects of the BMSCs are multiplied by the generated Tregs and M2 cells that release immune-suppressive factors like IL-10. The reported suppression of mast cells by BMSCs²⁶ might assist in controlling Type 1 hypersensitivity reactions and autoimmunity, while their support of neutrophil granulocytes²⁷ can be vital to prevent serious infections due to immunosuppression.

The interactions between BMSCs and immune cells and suggested molecular mechanisms are summarized in Fig 2.

BMSCs in GVHD

Acute GVHD is a serious complication of allogeneic hematopoietic stem cell transplantation (HSCT). This occurs in up to 30% to 90% of patients receiving HLA-matched sibling or HLA-mismatched unrelated donor bone marrow, respectively. Corticosteroids are the first line of treatment of aGVHD that, unfortunately, fail to induce remission in 20–50% of the patients²⁸. Clinical data support the safety of BMSC therapy in acute as well as chronic GVHD²⁹. Several case reports and Phase II studies suggest clinical efficacy while 2 larger Phase III trials failed to show a statistically significant therapeutic effect²⁸. There are many reasons for these discrepancies, such as exact characteristics of the cell product used as well as the timing, dosing, and the proper selection of patient population are all critical. While

better standardization of the therapy is needed, having many different therapy regimens might actually help us at this early stage to select the best treatment modalities for future patients. For a summary of the available GVHD clinical data see Table 2⁴⁷.

BMSCs and autoimmunity

Autoimmune diseases seem to be promising targets for the recently discovered BMSC immunomodulatory effects. The most widely studied of these autoimmune murine diseases is EAE or experimental autoimmune encephalitis, a preclinical model of multiple sclerosis^{30,31}. Treated mice showed a marked survival advantage along with decreased clinical disease activity and reduced histopathological scores. Stromal cell treated animals had reduced number of infiltrating immune cells, less apoptotic oligodendrocytes and less reactive astrogliosis in the central nervous system, while oligodendrogenesis and axon density progressively increased. After intravenous injection, BMSCs find their way to either the lymph nodes, or the CNS lesions where they exert their modulatory effect³². Using intravital microscopy and in vivo bioluminescence Constantin et al. suggested the importance of stromal cell activated VLA-4 (an α -4 β 1 integrin, the endothelial ligand for VCAM-1) in the first attachment step of BMSC homing to the inflamed nervous system³³. It is likely that other cell surface molecules contribute to the attachment/endothelial transmigration process of the BMSCs. Proving actual endothelial trans-migration of injected stromal cells is technically challenging, and most studies failed to demonstrate extravasation of these cells after systemic delivery. On the other hand, one must consider that BMSCs might not need to transmigrate at all in order to be effective. Initial immune cell interactions can happen within the vasculature in close proximity to inflammatory cells, by releasing an array of soluble factors. Once the first immune cell encounter takes place, the reprogrammed immune cells can “transmit the message” and facilitate a more distant anti-inflammatory response. Such interactions can happen between BMSCs and circulating monocytes, or regulatory T cells as demonstrated in our sepsis¹⁹ and asthma¹⁰ studies, respectively.

In addition to EAE, a number of other studies have shed light on various molecular mechanisms of the immunosuppressive potential of BMSCs in animal models of diabetes^{59–62}, arthritis^{34,35}, lupus^{36,37}, and colitis^{35,38–41}. Clinical data indicate effectiveness in multiple sclerosis, systemic lupus erythematosus, and Crohn’s disease (Table 3.)^{42,43}.

BMSC and fibrosis

Excess connective tissue - referred to as fibrosis - might form in virtually any organ in the human body. In some diseases such as idiopathic pulmonary fibrosis⁴⁴, fibrotic tissue formation seems to be the primary pathological abnormality, whereas in others, such as in liver cirrhosis⁴⁵, fibrosis is the result of a longstanding inflammatory process. Either way, replacement of normal tissue with a fibrotic component can be detrimental to the effected organ disabling its proper function.

Lung

Administration of cultured stromal cells can significantly attenuate the formation of fibrotic tissue. Ortiz et al. showed that delivery of BMSCs can inhibit inflammatory cell influx as well as collagen deposition in a bleomycin induced lung fibrosis model⁴⁶. Although the potential of BMSCs to transdifferentiate into lung epithelium was evident in this study, it is more likely that the beneficial effect was due to BMSC derived paracrine factors and/or direct cell-cell interaction between BMSCs and resident lung cells (or circulating immune cells). In a follow-up study the same group identified BMSC derived IL-1 receptor antagonist (IL1RN) as a major factor in the anti-fibrotic effect of BMSCs. IL1RN seemed to be critical in lowering the concentration of two fundamental proinflammatory cytokines: TNF- α and IL-1, both of which are implicated in the pathogenesis of bleomycin induced lung fibrosis⁴⁷. Moodley et al. showed that systemic injection of human (in this case umbilical cord derived) stromal cells - but not cultured lung fibroblasts - had considerable anti-fibrotic properties in a similar bleomycin model. Infused stromal cells homed to the lungs, and suppressed TGF- β production, SMAD2 signal transduction as well as the production of tissue inhibitors of matrix metalloproteinases, all of which define a pro-fibrotic milieu⁴⁸.

Liver

Zhang et al. used a carbon tetrachloride (CCL) induced liver injury/fibrosis model and studied the effect of amniotic membrane derived mesenchymal stem cells. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels (accepted markers of liver function) were significantly reduced in the treatment group and histological analyses of the liver showed less apoptotic hepatocytes, reduced collagen deposition and suppressed hepatic stellate cell activation - all of which indicate an attenuated fibrotic response⁴⁹. Another murine study by Zhao et al. used CCL or dimethylnitrosamine as liver toxic agents and found a significant survival advantage in their BMSC treatment group along with reduced number of myofibroblasts, cells implicated in the initiation and maintenance of excess extracellular matrix deposition⁵⁰.

Skin

Clinical reports suggest that BMSCs might be beneficial in systemic sclerosis, and chronic sclerosing GVHD, two debilitating fibrosing skin conditions.

BMSCs and tolerance induction

By suppressing immune responses responsible for graft rejection, BMSCs can prolong the survival of transplanted solid organs, or tissues^{23,51,52}. Underlying mechanisms include recruitment of regulatory T cells and a Th1/Th2 shift generating a Th2 dominant cytokine milieu. On the molecular level the tryptophan-catabolizing enzyme indoleamine 2,3-dioxygenase (IDO) known to suppress T-cell responses was proven to be critical⁵¹. In dermatology the tolerance inducing phenotype of BMSCs could be utilized to aid gene therapy, or allogeneic transplantation of skin fibroblasts and keratinocytes. There are several skin specific inherited abnormalities (genodermatoses) that can result in early death or disfiguring symptoms and poor life quality later in life. Skin adhesion defects is one of these

group, with Junctional Epydermolysis Bullosa and Recessive Dystrophic Epydermolysis Bullosa being the most likely candidates for gene therapy or allogeneic transfer of skin cells⁵³.

BMSCs in allergic conditions and sepsis

Although the initial efforts focused on identifying autoimmune diseases and sclerosing conditions as the primary targets of the newly discovered BMSC therapy it soon became evident that BMSCs can also suppress allergic responses and fight septic conditions. The observation that BMSCs shift the Th1/Th2 balance towards Th2 cells suggested that BMSCs could actually be harmful in Th2 dominant conditions (allergic diseases and some autoimmune conditions) but this assumption turned out not to be true. Using mouse models, our lab demonstrated in a ragweed induced allergic environment and Goodwin et al. in ovalbumin induced allergic airway inflammation that BMSCs are capable of suppressing Th2 responses either by collaborating with regulatory T cells or by increasing Th1 dominance^{19,54}. Thus the previously observed Th1-Th2 skewing effect is only licensed in Th1 dominant conditions. We also explored the possible therapeutic efficiency of BMSCs in a mouse model of polybacterial sepsis and discovered an interaction between the injected BMSCs and host monocytes/macrophages. The injected BMSCs are surrounded by innate immune cells that trigger the BMSCs to produce large amounts of prostaglandin E2 (PGE2). This factor then reprograms the pro-inflammatory (M1-TNF- α producing) monocytes/macrophages to become anti-inflammatory (M2) and produce high amounts of IL-10^{19,40,54}. These observations have since been confirmed by multiple groups⁵⁵ and some also found this mechanism to be essential in the suppression of murine autoimmune colitis, or in the wound healing effect of BMSCs⁵⁶.

BMSCs in dermatologic diseases. Which diseases are good targets?

A variety of immune mediated dermatologic conditions are likely to benefit from BMSC therapy^{57,58}. Diseases where effective therapy is lacking or cases that are resistant to conventional therapy should be targeted by BMSC therapy. If we consider the interactions that BMSCs have with cells of the immune system we might imagine which dermatological diseases could be potential targets of BMSC therapy. Based on data suggesting the suppression of T cell proliferation^{21–23}, diseases where T cells play a significant role could be targeted. These include psoriasis, contact dermatitis, or atopic dermatitis. Based on their effect on B cell function^{59–61} one can assume that pemphigus vulgaris and bullous pemphigoid could be affected by BMSC treatment. Finally, the regulation of mast cells by BMSCs⁶² suggest that urticaria and mastocytosis might also serve as feasible targets for BMSC therapy.

Also, when patients cannot continue immunosuppressive therapies because of deleterious side effects that resulted from direct organ damage (kidney, liver, bone marrow etc.) or from the massive immunosuppression. In fact, since BMSC therapy proved to be remarkably safe, with no serious side effects reported, we should weigh the possibility if in certain conditions BMSC therapy might even be used to replace immunosuppressive therapy right at the beginning of the disease. Another advantage of BMSC therapy is that these cells are not

purely immunosuppressive; they rather exert a complex immunomodulatory function. As we mentioned, in an infectious setting BMSCs turn M1 monocytes/macrophages into an M2 phenotype, which are known to be more efficient in eliminating bacteria. BMSCs also support neutrophil functions, attracting these cells to the site of infection (by secreting IL-8) and prolonging their survival once they arrived (with the use of the anti-apoptotic IL-6)^{62,63}. According to Krasnodembskaya et al. BMSCs are also capable of secreting LL-37, an anti-microbial peptide⁶⁴.

From a practical point of view one would want to choose a disease where clinical response is easy to quantify. Such a disease could be psoriasis with the often used PASI score⁶⁵. Psoriasis seems to be a logical target of choice, since the two major immune cell types that are affected by BMSCs play a major role in its pathogenesis. The role of T lymphocytes in psoriasis has been known for a long time^{66,67} while the importance of macrophages is a recent addition to our understanding of how psoriasis develops^{68,69}.

On the flip side of BMSC therapy it should also be mentioned that in certain diseases BMSCs might be harmful. Symptoms of neutrophil dermatoses⁷⁰ or cancerous growth, for example could even be worsened by the known supportive effect of BMSCs on neutrophil granulocytes or based on their immunosuppressive phenotype that can even promote the survival of tumors⁷¹.

Conclusion

Almost 10 years and more than 10.000 publications after Dr. Le Blanc's initial paper, we are starting to understand how BMSCs could be used most efficiently in the clinical practice. The initial enthusiasm stumbled upon conflicting data that surfaced about the efficacy of infused BMSCs in larger clinical studies. This in itself should not discourage the field due to a variety of reasons for failure and inconsistencies in some of the trials. Every day there are new molecules, novel immune cell interactions and conditions identified, many of which can fundamentally change the way we are thinking about the mode of actions of BMSCs. One of the most important realizations is that not all BMSCs are the same. BMSCs obtained from different donors can behave very differently. Race, age, gender, prior medical conditions, or medications taken by the donors can have a profound effect on the efficacy of BMSCs. BMSCs are a mixed population of cells and we need to improve our understanding of what all those sub-populations are and how to separate them. Some studies suggest, that even single cell derived colonies from the same person can in fact behave differently^{72,73}. Other factors are the method of collection (exact site of the bone marrow biopsy, amount of peripheral blood contamination in the sample etc.), culture conditions (different batches of Fetal Bovine Serum [FBS] affect growth and secretion profile of BMSCs) and the storage parameters of cells (cell density, cryopreservative etc.). We should also keep in mind that the hosts are different in all cases, too. Evidently, the same biologic parameters that can influence the donor cells can have an equally important effect in the selection of the right patient population we intend to treat. Disease specific immunological processes and concurrent immunosuppressive medications can also have a huge impact on the infused cells by triggering or inhibiting intracellular pathways critical for the immunomodulatory phenotype of BMSCs⁷⁴. Considering so many variables seems to be a disadvantage of

BMSC therapy but in fact can be a great opportunity, making cell therapy superior to single (or even multiple) agent drug therapies. We could not manufacture a drug that similarly to these living cells act like biosensors that can detect disease specific inflammatory fingerprints and then can deliver the most beneficial response to the host. BMSCs can also home to inflammatory sites and exert a concentrated effect on immune cells thereby lowering the chances of systemic side effects. We might learn in the future that by pre-treating (priming) BMSCs prior to systemic delivery with appropriate biological agents we can significantly improve their specificity and efficiency.

All these characteristics, together with the described donor variabilities can help tailor stromal cell therapy to individual patients and establish a superb personalized therapy. The road is long and bumpy, but the potential benefit to patients suffering from debilitating immunologic conditions is well worth it. It seems that BMSCs will open a new chapter in medicine by enabling an interactive cellular therapy that is governed by the unique diseased state of the patient while being free of any serious side effects.

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Biography

Dr. Krisztian Nemeth earned both his MD and PhD degrees from Semmelweis University, Hungary. He spent several years in the United States at the National Institutes of Health (NIH) in Dr. Eva Mezey's laboratory, where he studied the tissue regenerative and immunomodulatory potential of various bone marrow stem cell populations. Dr. Nemeth has published his findings in journals like *Nature Medicine*, *PNAS*, *Blood* and *Stem Cells*. In addition Dr. Nemeth has authored several review articles, book chapters and most recently a viewpoint essay in *Experimental Dermatology*. He also serves as an associate editor at the *American Journal of Stem Cells*. Dr. Nemeth has finished one year of clinical training in dermatology at Semmelweis University under the supervision of Dr. Sarolta Karpati. He is currently training at Boston Medical Center as a resident physician and also functions as a Special Volunteer at NIH and a Scientific Advisor at Semmelweis University.

BMSC subpopulations	Skeletal stem cells, transient amplifying skeletal progenitors, stromal fibroblasts
Culture characteristics	Plastic adherence, fibroblast - like appearance, large bright nucleus with small, grown in MEM -alpha with 10-20% FBS, no added cytokines or growth factors needed
Positive markers(human)	CD29, CD73, CD90, CD105, CD106, CD271, ALP, STRO-1, CD146 (only skeletal stem cells)
Negative markers	CD34, CD45, CD14, CD31
Differentiation test	Osteogenesis, adipogenesis and chondrogenesis
Immunosuppression test	Mixed lymphocyte reaction using PBMCs, or IL -10 measurement in a monocyte/macrophage co-culture
Alterantive sources of stromal cells	Cord blood, adipose tissue, amniotic membrane, gingival tissue, etc.

Fig 1.

Stem cell populations of the bone marrow and the progenies of skeletal stem cells are shown along with a summary of the most important characteristics of BMSCs. (The chondrogenic differentiation picture is a gift of Dr. Matthew Phillips)

During in vitro culturing the default cell type (labeled with pink background) is the skeletal fibroblast, which are the cells used in the clinical settings. Using specific media, the transit-amplifying progenitors can be differentiated towards osteogenic, adipogenic or chondrogenic lineage (blue background).

Fig 2.

Immunoregulation by BMSCs. BMSCs secrete several soluble factors (PGE2, NO, IDO etc.) that together can trigger generation of regulatory T cells and anti-inflammatory M2 monocytes/macrophages. In concert with these cells BMSCs can suppress the differentiation of antigen presenting dendritic cells as well as the functions of helper T cells, B cells, NK cells, and mast cells. By secreting IL-6 BMSCs can also prevent apoptosis of neutrophil granulocytes thereby supporting their antibacterial functions.

Table 1

Various names of BMSCs in the literature and corresponding number of hits in PubMed in July 2014

Name	Hits in PubMed
Mesenchymal stem cells	17581
Mesenchymal stromal cells	16195
Bone marrow stromal cells	3937
Bone marrow mesenchymal stem cells	2050
Mesenchymal progenitor cells	594
Multipotent mesenchymal stromal cells	324
Multipotent stromal cells	187
Bone marrow fibroblasts	183
Multipotent mesenchymal stem cells	174
Bone marrow mesenchymal stromal cells	174
Mesenchymal stromal stem cells	127
Bone marrow stromal stem cells	99
Skeletal stem cells	70
Skeletal progenitor cells	30
Multipotent mesenchymal progenitor cells	27
Bone marrow stromal fibroblasts	26
Bone marrow osteoprogenitor cells	24
Bone marrow multipotent stromal cells	9
Multipotent stromal stem cells	4
Bone marrow fibroblast-like stromal cells	2

Table 2

Summary of clinical experience with stromal cell therapy in GVHD.

Disease/Patient Number	Stromal cell source	Cell No. ($\times 10^6/\text{kg}$)	Dose/Patient number	Response	Reference
aGVHD (6) cGVHD (1)	Allo/BM	1.2	aGVHD 1 dose (6) cGVHD 2 doses (1)	aGVHD: Complete (5) No (1) cGVHD: No (1)	Ringden et al. ¹
aGVHD (55)		1.4	1 dose (27) 2 doses (22) 3 doses (4) 4 doses (1) 5 doses (1)	Complete (30) Partial (9) Stable (3) Progression (13)	Le Blanc et al. ²
aGVHD (3)	Allo/BM	0.5	1 dose (3)	No (3)	Arima et al. ³
cGVHD	Allo/BM	1.8	4 doses (2) 7 doses (1) 8 doses (1)	Partial (4)	Zhou et al. ⁴
aGVHD (10) cGVHD (8)	Allo/BM	1	1 dose (6) 2 doses (7) 3 doses (1) 4 doses (4)	aGVHD: Complete (1) Partial (6) No (3) cGVHD: Complete (1) Partial (3) No (4)	Perez-Simon et al. ⁵
aGVHD (2) cGVHD (3)	Allo/BM	2	1 dose (2) 2 doses (3)	aGVHD: Complete (2) No (1) cGVHD: Minimal (1) No (2)	Muller et al. ⁶
aGVHD (12)	Allo/BM	5	Between 2 and 21 doses	Complete (7) Partial (2) No (3)	Prasad et al. ⁷
aGVHD (13)	Allo/BM	0.9	Between 1–5	Complete (1) Partial (1) Minimal (5) No (6)	Von Bonin et al. ⁸
aGVHD (6)	Allo/BM	1	1	Complete (5) No (1)	Fang et al. ⁹
aGVHD (31)	Allo/BM	5	2	Complete (24) Partial (5) No (2)	Kebricai et al. ¹⁰
GVHD prevention (61)	Allo/BM	3	1	Lower incidence of aGVHD (14% vs. 30%) cGVHD (7% vs. 13%)	Balletal. ¹¹
GVHD prevention (25)	Allo/BM	0.8	1	Lower incidence of aGVHD and cGVHD (combined 11% vs. 53%)	Ningetal. ¹²
GVHD (refractory chronic) treatment	Allo/BM	0.6	1 dose (8) 2 doses (6) 3–5 doses (5)	Response in 73.7%	Wengetal. ¹³

Disease/Patient Number	Stromal cell source	Cell No. ($\times 10^6/\text{kg}$)	Dose/Patient number	Response	Reference
GVHD (chronic) treatment	Allo/BM	0.95	Average 2 doses (between 1–6) (22)	Significant improvement 3 months later in 12 patients	Weng et al. ¹⁴
aGVHD (40)	Allo/BM	1.5	Median of 3	Complete 27%, Partial 40%	Introna et al. ¹⁵
Co-transplant with HSC aGVHD (50)	Allo/UC	0.5	1 dose	66% progression free at 2 years	Wu et al. ¹⁶

aGVHD, acute graft versus host disease; cGVHD, chronic graft versus host disease; BM, bone marrow

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Table 3

Summary of clinical experience with stromal cell therapy in autoimmune diseases.

Disease/Patient Number	Stromal cell source	Total Cell No. (million cells)	Route	Response	Reference
Multiple sclerosis (10)	Auto/BM	8.8	1 (intrathecal)	Improvement (6) No change (4)	Mohyeddin et al. ¹
Multiple sclerosis (10)	Auto/BM	30	1 (intravenous)	Improvement (5) Stabilization (1) Progression (1)	Yam out et al. ²
Multiple sclerosis (15)	Auto/BM	63.2	1 intravenous and 1 intrathecal	Stabilization	Karussis et al. ³
Multiple sclerosis (3)	Mixed Alio and Auto/Adipose Tissue	42.6	Multiple intravenous and intrathecal	Improvement	Riodan et al. ⁴
Multiple sclerosis (1)	Allo/Umbilical cord	1/kg	Intravenous	Improvement	Liang et al. ⁵
Multiple sclerosis (10)	Auto/BM	29.5	Intrathecal	Improvement (4) Stabilization (12) Progression (6)	Bonab et al. ⁶
Multiple sclerosis (10)	Auto BM	1/kg	Intravenous	Improvement	Connick et al. ⁷
Crohn's disease, fistula (14)	Auto fat	40	1 intrafistula	Closure (71% vs. 16%)	Garcia-Olmo et al. ⁸
Crohn's disease, fistula (10)	Auto BM	20	Multiple intrafistula	Complete closure (70%) Partial closure (30%)	Ciccocioppo et al. ⁹
Crohn's disease (10)	Auto BM	1.5/kg	2 intravenous	Improvement in 2 cases	Duijvestein et al. ¹⁰
Crohn's disease (16)	Alio BM	2/kg	intravenous	Clinical response (12) Complete remission (8) Endoscopic improvement (7)	Forbes et al. ¹¹
Ulcerative colitis (39) and Crohn's disease (10)	Alio BM	150-200	intravenous	Clinico-morphological remission in 40 patients	Lazebnik et al. ¹²
SLE (15)	Allo/BM	1/kg	1 intravenous	Improvement	Liang et al. ¹³
SLE (16)	Allo/Umbilical cord	1/kg	1 intravenous	Improvement	Sun et al. ¹⁴
SLE (2)	Auto/BM	1/kg	1 intravenous	No change	Carrión et al. ¹⁵
SLE lung hemorrhage (1)	Allo/Umbilical Cord	80	1 intravenous	Improvement	Liang et al. ¹⁶
SLE (40)	Umbilical Cord	1/kg	2 intravenous	Major Clinical Response (13) Partial Clinical Response (11)	Wang et al. ¹⁷
Systemic sclerosis (1)	Allo/BM	1/kg	1 intravenous	Improvement	Christopeit et al. ¹⁸

Disease/Patient Number	Stromal cell source	Total Cell No. (million cells)	Route	Response	Reference
Systemic sclerosis (5)	Auto/BM	1/kg	1 intravenous	Improvement, mainly in skin ulcers	Kenyszert et al. ¹⁹
Polymyositis, Dermatomyositis (10)	Allo/BM and Umbilical cord	1/kg	1–2 intravenous	Improvement	Wang et al. ²⁰
Rheumatoid Arthritis (4)	Allo/BM	1/kg	1 intravenous	Minimal response	Liang et al. ²¹

BM, bone marrow; Allo, allogenic; Auto, autologous; SLE, Systemic Lupus Erythematosus; No, number

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