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Personalizing Stem Cell Research and Therapy: The Arduous Road Ahead or Missed Opportunity?

S.A. Patel^{1,2}, C.C. King², P.K. Lim², U. Habiba², M. Dave², R. Porecha², and P. Rameshwar^{2,*}

¹Graduate School of Biomedical Sciences, University of Medicine and Dentistry of New Jersey, Newark, NJ, USA

²Department of Medicine, Division of Hematology and Oncology, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, NJ, USA

Abstract

The euphoria of stem cell therapy has diminished, allowing scientists, clinicians and the general public to seriously re-examine how and what types of stem cells would effectively repair damaged tissue, prevent further tissue damage and/or replace lost cells. Importantly, there is a growing recognition that there are substantial person-to-person differences in the outcome of stem cell therapy. Even though the small molecule pharmaceuticals have long remained a primary focus of the personalized medicine research, individualized or targeted use of stem cells to suit a particular individual could help forecast potential failures of the therapy or identify, early on, the individuals who might benefit from stem cell interventions. This would however demand collaboration among several specialties such as pharmacology, immunology, genomics and transplantation medicine. Such transdisciplinary work could also inform how best to achieve efficient and predictable stem cell migration to sites of tissue damage, thereby facilitating tissue repair. This paper discusses the possibility of polarizing immune responses to rationalize and individualize therapy with stem cell interventions, since generalized “one-size-fits-all” therapy is difficult to achieve in the face of the diverse complexities posed by stem cell biology. We also present the challenges to stem cell delivery in the context of the host related factors. Although we focus on the mesenchymal stem cells in this paper, the overarching rationale can be extrapolated to other types of stem cells as well. Hence, the broader purpose of this paper is to initiate a dialogue within the personalized medicine community by expanding the scope of inquiry in the field from pharmaceuticals to stem cells and related cell-based health interventions.

Keywords

Graft-versus-host disease; immunosuppression; mesenchymal stem cells; microenvironment; personalized therapeutics

1. INTRODUCTION

The majority of treatments that are currently in clinical use are geared towards the general population, which can have unintentional effects in specific subgroups of patients. Personalized

medicine, by contrast, is based on targeted therapeutic approaches that allow for patient-specific care [1]. The overarching goal of personalized medicine is to maximize the therapeutic potential of health interventions while minimizing the risk for adverse effects. Cellular therapy, in particular, warrants a personalized approach because of the multitude of interactions between donor and host that can decisively influence treatment outcomes [2]. As basic science findings and knowledge on stem cell biology continue to accumulate, questions are now emerging on how best to translate the existing stem cell research platforms towards therapeutic applications that have predictable and adequate clinical effectiveness and safety. Ideally, the precise planning of stem cell delivery must be coordinated together with the target characteristics of individual patients in order to fully harness its therapeutic potential [3]. The entire process, from patient profiling to delivery and maintenance of successful stem cell therapy, will undoubtedly require a multi-dimensional and thorough understanding of the numerous factors that impact research and treatment outcomes.

Several important considerations arise from the personalized use of stem cells for therapeutic purposes. Host factors, donor factors, and the overall environment in which the stem cells function must be collectively taken into account to understand the variable outcomes associated with stem cell based health interventions [4]. Indeed, there exists substantial person-to-person and population differences in the out-come of stem cell therapy [5-7]. This is not surprising since differences among humans in physiological function and tissue microenvironments can lead to vastly different effects from stem cells. Ethnicity-specific correlations have also been determined in assessment of patients' overall functioning [8]. Apart from these factors, the source of stem cells must also be carefully chosen based on functional and physical criteria that lead to optimal outcomes [4]. For example, the use of autologous cells, such as one's own inducible pluripotent stem cells for the treatment of hematological conditions, is complicated by the possibility of cellular transformation [4].

One of the most complex physiological systems in the body is the immune system, which serves to protect the host against foreign antigens. Perhaps the most well known inter-action between stem cells and host physiology involves immunological factors. These interactions are important especially under immunopathological conditions [9,10]. The host immune response involves interactions with foreign antigens that can influence, and be influenced by, stem cell therapy [11]. The use of stem cell therapy in the context of immunology will be discussed in this paper since it has far reaching implications in personalized medicine. We note that the field of personalized medicine should include broader considerations on how best to individualize stem cell therapy, beyond the traditional limited focus on small molecule drugs. In particular, we explain the promise and the possibility of polarizing immune responses to rationalize therapy and improve benefits from stem cell interventions in individual patients. We also present the challenges to stem cell delivery in the context of the host related factors.

2. STEM CELLS AND IMMUNOLOGICAL PHENOMENA

The use of tissue-specific stem cells for repair of dysplastic or degenerative disorders has been traditionally attempted for the same organ of their origin. Hematopoietic stem cells (HSCs), for example, benefit disorders of hematologic etiology based on their ability to generate blood cells and to reconstitute an ablated immune system [12]. As another example, neural stem cell therapy has been proposed as treatment for disorders of the central nervous system [13]. Mesenchymal stem cells (MSCs) have been shown to facilitate the recovery of bone, adipose, cartilage and connective tissue [14-16].

MSCs differ from other stem cells with regards to their repair potential, based on their immune properties. These functions have implications that extend beyond their immediate effects of tissue regeneration. Aside from their ability to generate connective tissue elements, MSCs can

remarkably escape immune recognition and exert immunomodulation, making them an attractive alternative to conventional immune suppressants, which have adverse effects [17]. The elucidation of immune modulatory mechanisms of MSCs is therefore critical for the development of treatment protocols, tailored to an individual patient. The diversities of potential responses to MSCs or any other stem cells preclude the establishment of a single clinical regimen for a particular disease [18].

2.1. Immunosuppression by Mesenchymal Stem Cells

The immunoregulatory properties of MSCs are well known based on both *in vitro* and *in vivo* studies (Table 1).

The mechanisms of MSC-mediated immunomodulation are diverse and interconnected [18-19]. For example, MSCs have been shown to suppress allogeneic responses and exert nullifying activity in mixed lymphocyte reaction [18,20]. With regard to the T-helper 1/T-helper 2 (Th1/Th2) lymphocyte balance, MSCs favor generation of Th2 subsets in murine models of graft-versus-host disease (GvHD) [11]. MSCs also demonstrate inhibitory effects on other cells of the lymphoid lineage, such as B cells and NK cells [21]. MSCs interfere with and facilitate immune signaling by altering expression of chemokine ligands and receptors [22]. Studies on the effects of MSCs on the induction of regulatory T cells (T_{regs}) have demonstrated a facilitative role, and further studies on this emerging concept are currently underway [23]. These investigations highlight only a fraction of the basic science knowledge that has accumulated on the immunological properties of MSCs. Since the specific mechanisms of immunosuppression by MSCs are out of the scope of this review, we will turn our attention to the implications of immunomodulation as they pertain to personalized medicine.

The *in vivo* significance of immunomodulation by MSCs has been demonstrated in various disease models of inflammation and autoimmunity. Co-transplantation of MSCs has been shown to promote cardiac engraftment and enhance graft survival [19,23]. Adipose-derived MSCs show therapeutic benefits in murine models of inflammatory bowel disease [24]. These types of findings underscore the potential therapeutic applications for stem cells, including their use in the treatment of degenerative tissue damage. MSCs show therapeutic benefit for autoimmune and inflammatory diseases [25,26]. Translation of MSCs for these two immune-mediated disorders is currently under intense investigation, as the data are still equivocal. The *in vivo* outcome of these studies have led to the establishment of clinical trials due to evidence that MSCs show efficacy in suppressing inflammation and immune effector responses in patients. Nonetheless, the safety and efficacy of MSCs remain to be established in further clinical studies.

2.2. Immunostimulation by Mesenchymal Stem Cells

Although MSCs demonstrate suppression on the immune system, they can also exert immunostimulation. This latter property of MSCs cannot be disregarded when therapies are planned since MHC class II expression in MSCs can lead to immune rejection and, if autologous, immune activation [10]. IFN- γ has a key role in regulating MHC class II expression in MSCs even though the effect is bimodal with reduced MHC-II expression at high IFN- γ levels [10]. Since IFN- γ is a critical component of macrophage activation and other immune effector responses, it is difficult to predict how stem cells will react within a milieu of cytokines and immunological mediators. Furthermore, some studies demonstrate an immune-enhancing effect of MSCs on B cell proliferation [21]. Indeed, recent information on the outcome of MSC trial as third party stem cells for GvHD attests to the need to incorporate the principles of personalized medicine [6,7].

It is important to consider that there are differences among patients for any particular immune response identified thus far. At this time, generalizations for an expected outcome on MSCs cannot be made for the population as a whole. The limitations of isolated experiments must be overcome if stem cell therapy is to achieve success in clinical trials [27]. Based on these premises, the need for personalized medicine approaches to stem cell therapy is clear.

2.3. Implications for Personalized Medicine

Considering the immunomodulatory properties of MSCs alone, an argument for stem cell personalized therapy can be made on numerous grounds. The heterogeneity in physiological responses to stem cells can be accounted for by factors including the source of the donor stem cells, the nature of disease, progression of disease, and the patient profile [28]. Patient profile can be further subdivided into factors that include age, sex, past medical history, and overall health (Fig. 1) [28]. Each of these factors can contribute to variations in the response to stem cell treatment from person to person. Both genetic and environmental factors can have unpredictable effects, meriting the study of tailored stem cell therapy. Therefore, it is not surprising that recent clinical trials using stem cells have not reached unequivocal success.

Although numerous breakthroughs in stem cell research have been made thus far, their success and applicability in clinical trials remains to be ascertained. A recent report on MSCs as third party cells for GvHD showed promising results in some cases, but unexpected negative results in other analyses [6,7]. These findings highlight the convoluted nature of stem cell therapy and remind scientists that a complete understanding of basic science is fundamental prior to and during implementation of these cell-based interventions in the clinic.

The study of stem cells *in vivo* poses significant challenges due to various microenvironmental factors that can have unintentional effects (See Section 7). *In vitro* studies, on the other hand, generally bypass this dilemma since the investigator exerts greater control over the experimental conditions, but the application of *in vitro* findings must eventually be confirmed and verified *in vivo* before translation to patients. It is critical to conduct *in vitro* stem cell research with caution because challenges can frequently re-surface when experiments are conducted in human subjects.

3. CELL FATE SPECIFICATION OF MESENCHYMAL STEM CELLS

MSCs are attractive for cell therapy due to their ease of expansion *ex vivo*, and their potential to generate cells of all three germ layers [29]. Hence, MSCs can generate bone, cartilage, adipose, stroma, neurons, and cardiac myocytes [15,16,30]. In light of these findings, many scientists have revoked the previous notion that MSCs are multipotential in favor of emerging evidence indicating the *pluripotency* of MSCs [15,16].

3.1. Chemical Factors Determining Cell Fate

The specification of cell fates of MSC has undergone extensive studies. Their differentiation can be induced by specific agents. Treatment with 5-azacytidine, for example, can lead to specification of an osteogenic phenotype or cardiac myocyte-like phenotype [31-33]. While the mechanisms of development could be complex and dependent on interactive effects, epigenetic changes, such as DNA methylation appear to be important [31,34]. In other studies where epigenetic changes are not reported, this could be implied. As an example, treatment of MSCs with retinoic acid and basic fibroblast growth factor (bFGF) has been shown to induce neuronal specification, through the process of transdifferentiation [15,16]. While DNA changes have not been reported, genes known to suppress the expression of neuronal genes have been downregulated upon maturation to neurons [15,16,35]. This suggested that DNA modification might have occurred to prevent interactions with the genomic DNA of the neuron-associated

genes. In other studies, treatment of MSCs with other inducing agents, sonic hedgehog (SHH), bFGF, and fibroblast growth factor 8 (FGF8), also caused transdifferentiation to neurons, but of a different subclass – dopaminergic [36].

Osteogenic induction of MSCs can occur *via* treatment with β -glycerophosphate, ascorbic acid, and/or platelet lysate [34,37]. On the other hand, adipogenic differentiation requires treatment with dexamethasone [34]. TGF- β family members and collagen-based hydrogels can specify a chondrogenic fate [38,39]. In the absence of specific cocktails of soluble factors, MSCs have been shown to differentiate into adipose tissue and stroma [40]. Table 2 illustrates a representative example and summary of the developmental specification of MSCs to various cell types.

3.2. Physical Factors Influencing Cell Fate

Aside from soluble factors, mechanical and physical factors can also specify stem cell fate. For example, the contact surface onto which MSCs are seeded or delivered can regulate differentiation programs. Ectopic osteogenesis *via* MSCs occurs on a ceramic scaffold *in vivo* [37]. The force of gravity also appears to have an effect on stemness in MSCs, as gravity can induce MSCs to differentiate into force-sensitive cells like cardiac myocytes and osteoblasts [34,41]. As pertaining to personalized medicine, individual patients have different levels of shear stress and matrix rigidity within their bodies, and the effects of MSCs can thus vary with these differing physical forces [34]. Different types of matrices have been shown to have consequences on MSC proliferation and adhesion. The three-dimensional scaffold plays an important role in stem cell delivery and maintenance [30]. By no means are these findings comprehensive since evidence accumulates rapidly in this dynamic field that could benefit substantially from further engagement with research in personalized medicine.

3.3. Implications in Personalized Medicine

Clearly, the therapeutic implications of MSCs extend far beyond their ability to produce bone, cartilage, adipose, and stroma. The field of stem cell transdifferentiation for therapeutic purposes is in its infancy but holds much promise for treatment of degenerative disorders of various systems based on these seminal findings. In light of the fact that MSC fate can be specified by both soluble and mechanical factors, it would be beneficial for the field to integrate principles of cellular biology, molecular biology, and bioengineering, since these disciplines will eventually apply to patient-oriented research when MSCs are implemented in the clinic [41].

4. AUTOLOGOUS VERSUS ALLOGENEIC STEM CELL TRANSPLANTATIONS

The use of allogeneic and autologous transplantation has experienced success in the clinic [42]. Stem cell transplants have emerged as rather successful therapeutic options for a multitude of diseases, such as those of hematological origin where the hematopoietic system is replaced. Hurdles to allogeneic transplantation involve rejection of donor cells and development of GvHD [11]. Comparisons between allogeneic and autologous transplant therapies have demonstrated the critical role of the immune system in determining clinical outcomes. Autologous transplants bypass some of the complications of allogeneic transplant because autologous transplants do not significantly stimulate the immune response [18]. However, in cases where there is a need for immediate treatment with stem cells, it will not be practical to wait for *ex vivo* expansion and re-transplantation of autologous stem cells [18]. Examples include acute injuries, such as traumatic brain injury, spinal cord injury, and other pathologies.

The treatment spectrum for autologous and allogeneic therapy differ based on the disease type. In the case of hematopoietic replacement or reconstitution, autologous stem cell therapy has

found the most success as the main therapy in several hematological disorders, such as multiple myeloma and malignant lymphoma [42,43]. During autologous transplant, host stem cells are harvested and cryopreserved prior to chemotherapy treatment, then re-administered, preventing damage to the host stem cell pool [28,42,44]. Allogeneic stem cell therapy has been more useful for treatment of acute leukemias, aplastic anemia, and hereditary hemoglobinopathies [28]. While sharing similar clinical outcomes with allogeneic transplants, autologous transplants may be impractical if healthy stem cells were not extracted from patients prior to initiation of therapy. GvHD, an immunological complication affecting many organ systems, continues to be one of the major drawbacks of allogeneic stem cell transplantation, not only by HSCs, but also other stem cells. An understanding of the induction or prevention of GvHD by particular stem cells is critical to gain a comprehensive understanding on how stem cell transplants can be applied as a form of personalized medicine.

Target organ damage in GvHD appears to occur primarily *via* T lymphocytes and involves two independently working pathways: CD4+ and CD8+ T cells, both with significantly different mechanisms of action [45,46]. CD4+ T-cells employ the Fas (CD95)/FasL (CD95L) lytic pathway, whereas CD8+ T cells employ the perforin/granzyme B pathway [47,48]. Despite these differences, the commonality by these different cell types involves cytokine-mediated toxicity. IL-2 and TNF- α production by CD4+ cells occurs within days of transplant contributing to increased mortality [46]. Rejection, on the other hand, often correlates with expression of IFN- γ in allografts [45]. The severity of GVHD is partly determined by donor T-cell fraction [46]. Thus, immunological parameters that differ among donors can play an unpredictable role in treatment outcomes.

4.1. Employment of Mesenchymal Stem Cells for Graft-versus-Host Disease

Plans to use MSCs as suppressors of GvHD were entertained since current treatments show limited efficacy with significant adverse effects. Non-stem cell therapy for GvDH includes delivery of corticosteroids, methotrexate, mycophenolate mofetil, antithymocyte globulin, and non-steroidal anti-inflammatory agents [49-51]. Corticosteroids in particular have been a mainstay for therapy. While steroids can reduce the severity and incidence of GvHD, they can cause complication through untoward effects, such as increased risk of infection, glaucoma, cataracts, weight gain, and bone loss [52]. MSC therapy is intended to cause similar outcome of the anti-inflammatory agents while bypassing untoward effects. The current conventional treatments for GvHD do not take into account the individual molecular and other profiles of patients. Personalized stem cell therapy would allow for tailored treatment with maximal efficacy and limited adverse effects. The success of future personalized stem cell therapy will depend on current endeavors to apply these cells in the context of principles of pharmacogenomics, among other indicators.

An understanding of the immune advantages and disadvantages of autologous transplants was provided by decades of experience with the bone marrow transplants. The possibility of reducing GvHD led to enthusiasm of initial studies on autologous transplants in which the transplants were performed in combinations of immune- and chemo-therapy. Seminal investigations on bone marrow transplants for treatment of radiation exposure in mice demonstrated that autologous transplants did not lead to host tissue destruction by donor cells, in contrast to allogeneic transplants. In terms of cure, both treatments resulted in cure of radiation-induced aplasia [53,54]. Despite the reduced incidence of adverse effects by autologous transplant, the benefits are confounded with higher frequency of relapse as compared with allogeneic stem cell transplants [54,55]. This difference in outcome is likely due to loss of graft-versus-tumor effects, a process that would be absent with autologous transplants. The beneficial anti-tumor effect of donor cells presented a challenge for autologous transplants. These studies have been explored in the past and are currently underway [56].

Taken together, the findings have profound implications in the implementation of stem cell therapy for GvHD. Their abilities to home to sites of inflammation, escape immune detection, and demonstrate immunosuppressive and anti-inflammatory effects make them ideal for various disease states.

4.2. Lessons from Clinical Trials

Despite the well-established properties of MSCs in the laboratory, the recent clinical trials have shed novel insight into the limitations of cellular therapy for GvHD. These clinical trials reached late stages but failed, demonstrating that for example, the human adult stem cells had no significant efficacy over placebo in alleviating skin manifestations of GvHD [5]. However, therapeutic benefit was observed in gastrointestinal and liver manifestations [5]. Scientists have learned much from the outcomes of the latter clinical trial. Firstly, the results of these clinical observations have reinforced the basic idea that *in vitro* properties do not always correlate with *in vivo* efficacy, as *personal microenvironmental* factors can have profound influences of cellular behavior [57]. The failure of this clinical trial warrants investigations into a personalized approach to stem cell therapy based on optimal conditions for each patient. Nonetheless, the field is still evolving, and single clinical failures should not interfere with the overarching favorable evidence that has accumulated thus far.

5. GRAFT-VERSUS-TUMOR EFFECTS IN STEM CELL THERAPY

As discussed above, the benefit of autologous stem cell transplantation is the circumvention of immune rejection. However, in the event that there is an underlying malignancy in the host, autologous transplant will fail to elicit graft-versus-tumor effect to eliminate the tumor cells. This process has been described for leukemia patients undergoing bone marrow transplantation [58]. Attempts to harness the beneficial effects of the graft-versus-tumor effect while minimizing GvHD involve the use of both single-agent and cellular therapy [58]. For example, bortezomib is effective in inhibiting the progression of GvHD by inhibiting proteasome and NF- κ B signaling [59]. Bortezomib treatment inhibited cytokine signaling and enhanced sensitization of tumor cells to lysis, thereby facilitating graft-versus-tumor effect [59].

Suberoylanilide hydroxamic acid inhibits histone deacetylase activity and hinders GvHD *via* immunosuppression *via* cytokines [60]. This agent preserves the graft-versus-tumor effects [60]. Regarding cellular therapy, T-cell depletion from allografts and subsequent immune enhancement has been proposed [61]. In addition, there is proposal to alter the balance between Th1 and Th2 responses [61]. These discoveries shed insight into ideas about harnessing the beneficial aspects on stem cell therapy while limiting the adverse effects. A thorough comprehension of the immunology of stem cells is needed to make the science of cell therapy more efficient as the field progresses.

6. HETEROGENEITY AMONG STEM CELLS

Traditional views in stem cell biology held that one particular tissue type arises from one particular stem cell. For example, the sole source of neurons was originally thought to be neural stem cells. As evidence on transdifferentiation and stem cell plasticity amounts, the traditional views are fading away in favor of more complex themes involving cross functions of stem cells.

6.1. Variability among Mesenchymal Stem Cells

The effects of environmental factors on MSC behavior are diverse and can include alteration of gene expression signatures within distinct MSC populations. This finding lends credibility to new ideas on personalized stem cell therapy [62,63]. A single standard method of culturing and expanding MSCs has not been established, and therefore evidence on MSCs from current

literature may be difficult to interpret based on different culture conditions. Furthermore, the bone marrow microenvironment varies from person to person due to multiple factors, including genomic differences and overall health. Based on these differences, it is likely that the MSCs, as used in clinical and experimental studies, could be heterogeneous and this might account for the differences in the literature. Analyses of experimental results with MSCs from different donors may lead to misinterpretations. Human MSCs show donor differences with regards to the gene expressions, despite similarities in isolation protocols [63]. Pronounced variations can emerge as sparse cultures become confluent and are expanded by serial passage while they approach senescence [63]. Therefore, generalizations about the effect of MSCs are difficult until variations among donors are elucidated.

6.2. Hematopoietic Stem Cells

Aside from MSCs, HSCs also harbor heterogeneity. The bone marrow is the major source of HSCs, but HSCs can also be derived from other places, such as peripheral blood and umbilical cord blood. These latter sources appear functionally superior with regards to recovery in granulocytes and thrombocytes as compared to similar cells from bone marrow [64]. T-cells derived from the umbilical cord blood are immunologically naive and show functional differences with regards to engraftment. The use of umbilical cord blood-derived HSCs may lead to better immune reconstitution than the use of other HSC sources, and the incidence of GvHD may be less with the use of umbilical cord blood-derived HSCs [64]. Thus, the bone marrow, peripheral blood, and umbilical cord blood are all valuable sources for HSCs for stem cell therapy, and each provides its unique benefits and obstacles.

7. MICROENVIRONMENT AND STEM CELLS

There are several other reasons to suggest that the implementation of personalized medicine with stem cells is required. A major rationale is based on variations among microenvironments, which could be influenced by the patients' ethnic background as well as other underlying clinical disorders. Thus, the functions of stem cells could be different in each host. Slight variations in the locale of stem cells can have significant impacts in clinical success. Stem cells have particular niches in which they thrive best. Thus, microenvironmental considerations cannot be overlooked prior to the implementation of stem cell therapy. The microenvironment can determine the long-term ability of MSCs to stably integrate into host tissue.

The composition of the microenvironment and the presence of certain soluble factors are major determinants in the stable differentiation of MSCs. In the laboratory setting, the plasticity of MSCs has been elucidated through their ability to transdifferentiate into ectodermal and endodermal cell types depending upon the cytokines and growth factors provided in culture [16,35,65-67]. The success of these findings in a clinical context is limited, however, by the fact that *in vitro* conditions are carefully monitored and manipulated in the laboratory. *In vivo*, transplanted MSCs would develop under the discretion of paracrine factors in the cellular environment which may result in beneficial or undesirable outcomes. Therefore, the results obtained *in vitro* do not ensure that transplanted MSCs will provide the desired therapeutic results *in vivo*.

In an individual, microenvironments are not uniform among tissues, within tissues and organs; thus one must ascertain an in-depth understanding of the microenvironmental factors that would be expected at relevant sites. For example, in bone marrow, MSCs first begin to develop in an area that is relatively replete with oxygen, close to the central sinus [68]. As MSCs migrate towards the endosteum, which is relatively hypoxic, the stem cells differentiate into stroma/fibroblasts [68]. The presence of an *oxygen concentration gradient* and subsequent differentiation of MSCs within bone marrow is a classical example of a specific local microenvironment found within a given tissue. Other possible sites of MSC transplantation

and homing include the abdominal viscera, heart, and central nervous system, with each providing a unique microenvironment that can affect the outcome of therapy [23].

Of additional importance is the effect that MSCs will have on the microenvironment after their transplantation in a specific tissue. MSCs express many cytokine receptors and their interaction with cytokines can result in an immunoregulatory role of MSCs *via* the additional release of other soluble factors by MSCs or cellular contact [57]. Stimulation of MSCs by the pro-inflammatory cytokine interleukin-1 α (IL-1 α) can facilitate differentiation, depending on the inducing agent [15]. Upon differentiation, the cells begin to release factors, different from the injected stem cells. Thus, the functions within the site of transplantation will change with time. Since some of the newly released factors could be immunoregulatory, the resulting microenvironment could elicit or inhibit immune responses such as lymphocyte proliferation, enhanced phagocytosis, eosinophil migration, mast cell degranulation, and fibrosis [69,70]. Inflammatory factors, such as IFN- γ can cause an upregulation of the co-inhibitory marker B7-H1 to suppress T-cell proliferation [71]. This represents an example of how information on cytokines at the region of tissue damage could assist in determining the functional outcome of MSC transplantation.

Microenvironmental factors can also have unforeseen effects on the differentiation of stem cells. For example, pro-inflammatory signals can suppress chondrogenic differentiation of MSCs [72]. IL-1 β and tumor necrosis factor- α (TNF- α) exert dose-dependent inhibition of cartilage formation by MSCs [72]. High levels of cyclooxygenase, an enzyme that leads to production of various mediators of inflammation, can cause de-differentiation of chondrocyte [73]. Frequently, patients who require cartilage for tissue repair are those with inflammatory conditions, e.g., osteo- and rheumatoid arthritis. These types of inflammatory microenvironment could nullify the therapeutic benefit of MSCs. Similarly, the use of MSCs for repair of ischemic cardiac damage could lead to cell death [74]. Pharmacological preconditioning has been suggested as a means to evade MSC death upon delivery to the ischemic tissue [74]. However, the nature of the infarcted microenvironment and the degree of ischemia likely varies among patients, based on patient age and disease severity; otherwise it would be difficult to predict the therapeutic outcomes of stem cells.

Given the above argument, it appears that personalized treatment regimens with MSCs would require an understanding of the cellular interactions with the *prospective microenvironment*. Through this information, therapeutic outcome of MSCs, and other stem cells, would be better predicted. The uniqueness of each individual requires a molecular understanding of the microenvironment in order to ensure that signaling molecules and cellular interactions will provide desirable results.

Another dimension that confounds stem cell delivery is timing of signals. Timeline is critical in order for stem cells to exert maximal beneficial effects, but current evidence is not well supported regarding when particular signals must be present in order for clinical benefits to be optimal [57]. In the absence of such information, the microenvironment may still lead to the development of significant deleterious effects with the use of personalized MSCs therapy.

8. OTHER STEM CELLS IN PERSONALIZED TREATMENTS

While we focused on the MSCs in this paper, these lessons are relevant for other stem cells as well. For example, stem cells from the dental pulp have been proposed for personalized therapy to promote proliferation of endogenous host neural cells [75]. These cells share properties of MSCs and, through a personalized approach, may conceivably bypass immunological complications [75]. Dental pulp stem cells have been shown to modulate the microenvironment of the engraftment site and facilitate recruitment of endogenous neural progenitors. In addition, multipotential adult progenitors from skin and adipose are now receiving attention, as they can

be used efficiently in autologous therapy based on the ease of isolation [76]. These findings have implications in treatment of states of cellular insufficiency or tissue degeneration.

The prospect of using neural stem cells for personalized cell therapy has received recent attention. Neural stem cells have a propensity to migrate to the brain [77]. The phenomenon of neural stem cell transduction for gene delivery is emerging. Neural stem cells can be transduced with genes and serve as therapeutic vehicles with targeted effects [78]. For example, the anti-proliferative effect of interferon- β (IFN- β) can be harnessed by loading neural stem cells with this gene and allowing these cells to migrate naturally towards sites of tumor [78].

Genetic engineering of neural stem cells for the treatment of metabolic defects has been successful [77]. Neural stem cells have been used to treat Tay-Sachs disease *via* restoration of hexosaminidase A enzyme, which degrades GM2 gangliosides [79-81]. Based on these findings, it is reasonable to propose neural stem cells as cellular vehicles of enzymes to treat biochemical or metabolic disorders of the brain. In Sandhoff disease, characterized by deficiency of hexosaminidase B, bone marrow transplant resulted in increased hexosaminidase B levels [82]. It would be reasonable to suggest that transplants that combines neural stem cells and bone marrow could synergize to restore biochemical defects. It is important to recognize the outcomes of a recent study employing neural stem cell therapy, during which a patient with ataxia telangiectasia developed multifocal brain tumor after administration of fetal neural stem cells [83]. Tumor development after years of disease-free survival supports *in vitro* evidence of cancer-initiating phenotype and malignant transformation of stem cells [83].

9. CHALLENGES TO PERSONALIZED STEM CELL THERAPY

9.1. General Considerations

The interesting aspect about pharmacogenomics concerning stem cells as a therapeutic option is that, unlike for typical small molecule drugs, prediction of treatment responses to stem cells depends on interactions between the delivered stem cells and the cells of the host.

Pharmacological responses to single agents such as drugs are relatively straightforward compared to responses to stem cells since cell-based therapy is far more complex, and host-dependent than therapy with compounds [84]. The plethora of biological properties inherent to MSCs, as described in this report, requires consideration of all possible interactions they can have with host systems. Understandably, such considerations may lead one to cast doubt on their clinical utility. In addition, the low efficiency of stem cell differentiation into target cell types must be overcome by establishment of definitive differentiation protocols. Physical factors, such as scaffolding and gravity, play an important role in MSC differentiation, and the lack of optimal mechanical parameters can hinder success [85].

Non-biological concerns include socio-political factors that may hinder the implementation of personalized medicine. Issues concerning reimbursement of current technologies used in personalized medicine, for example, have limited the development of marketed products [86]. The premium cost of personalized services and therapies is a topic of heavy debate in health policy [86]. There is currently a need for enhanced clinical evidence of the benefit of personalized medicine in order for marketed products to achieve coverage [86]. Furthermore, inclusive support from all members of the society and stakeholders would help foster successful reimbursement plans and coverage of patients, allowing for more efficient transition into personalized health plans [87].

9.2. Tumorigenicity in Stem Cell Therapy

Aside from the immunological properties discussed previously, MSCs have been associated with tumor formation. Malignant histiocytoma can arise from MSCs with Wnt pathway defects [88]. Retroperitoneal sarcomas and dermatofibrosarcoma, although rare, have also been shown

to arise from MSCs [89,90]. The propensity to form these tumors likely varies among patients based on their genetic predisposition for cancer. MSCs not only serve as the source of certain tumors, but also facilitate growth and development of tumors of non-mesenchymal origin. For example, MSCs can enhance breast cancer metastasis *via* degradation of cell-surface anchorage proteins like E-cadherin and secretion of trophic cytokines like CCL5, also known as RANTES [22,91]. The reciprocal interaction between MSCs and breast cancer cells involves tumor-mediated induction of CCL5 from MSCs, which in turn enhances motility of breast cancer cells [22]. Furthermore, the production of stroma by MSCs can have lethal consequences in the face of epithelial malignancies because stroma and carcinoma-associated fibroblasts have supportive roles in cancer progression [91,92]. It is nearly impossible to predict whether or not MSC therapy will lead to overt malignancy in each patient. The lessons learned from the field of pharmacogenomics and personalized medicine thus might play an important role in safe and effective delivery of MSCs. Neural stem cell therapy is also complicated by the development of donor-derived tumors years after transplantation [83].

9.3. Challenges with Embryonic Stem Cell Therapy

Although the potential benefits of personalized stem cell therapy are vast, as discussed above, implementation of personalized therapy must first overcome other significant obstacles. Perhaps the most obvious challenges to personalized therapy for embryonic stem cells (ESCs) revolve around immunogenicity, which can lead to rejection of implanted cells. Thousands to millions of ESC lines must be used to accommodate genetically diverse patient populations [93]. The generation of such a large number of ESC lines would be impractical considering the ethical and scientific limitations to harvesting these cells [94]. Ideas on the creation of a universal ESC line have been proposed to bypass some of these problems, although such an approach may not be feasible in practice.

In order to ensure delivery of healthy stem cells, the cell population must be purified prior to delivery into the host because mutations in the genome can lead to development of tumors, such as teratomas [95]. However, the purification process may induce unforeseen genetic damage, and quality control must be performed before delivery to the host [93]. Creation of a reliable source of stem cells may be more difficult than previously thought [96]. Transmission of infection by ESCs may also limit their use [93]. ESCs are immunogenic as evident by MHC expression, and MHC expression is increased when ESCs lose their pluripotency [95]. Hence, MHC antigens must be matched as closely as possible to minimize rejection [95].

Aside from the biological challenges to the employment of ESCs in personalized medicine, numerous ethical issues emerge. The source of ESCs is the inner cell mass, which is located in the blastocyst of a zygote. Adult stem cells, on the other hand, bypass these problems because they can be obtained readily from the bone marrow [20]. Thus, therapeutic avenues that arise from MSC and HSC research may address some of the attendant socio-ethical concerns more effectively compared to ESC investigations.

10. CONCLUSIONS AND FUTURE OUTLOOK

Clearly, the field of stem cell therapy needs research that would serve towards the purpose of individualized treatments. The variety of factors that influence disease prognosis and clinical outcome could vary based on genetic variations. Pharmacogenomics principles and lessons, too, could be incorporated in the field of stem cell therapy. Genomic tools such as microarray analyses could be used to determine which treatments will offer maximum therapeutic effect and minimal adverse effects as the stem cell therapy edges towards clinical applications [1]. High-density genomic microarrays can assess global changes in mRNA and protein expression in patients and can give insight into epigenetic processes [97]. These technologies should be employed in a way to allow for the calculation of pharmacogenomic risks, anticipation of

adverse drug interactions based on an individual's metabolism, and prediction of therapeutic outcomes [98]. Alongside these emerging biotechnologies, current bioinformatics approaches can be incorporated into basic science research to enhance the identification of molecular differences that merit a personalized approach to certain diseases [97]. These studies will allow for a fundamental redefinition of disease at the molecular and cellular levels as they relate to subsets of patients with similar characteristics [1]. *In vivo* cellular imaging, such as for detection of single-cell metastases, may allow for early diagnosis of disease. Cells can be labeled with probes and detected using current imaging technology, and this can in turn allow for determination of cellular trafficking and homing abilities in individual patients [99].

Although we concentrated on the mesenchymal stem cells in this article, the overarching rationale can be extrapolated to other types of stem cells as well. Hence, the broader aim of this paper was to initiate a dialogue within the personalized medicine community by expanding the scope of inquiry in the field from pharmaceuticals to stem cells and related health interventions.

In summary, the studies in the emerging field of personalized stem cell research and therapy will require teams of multi- and inter-disciplinary scientists to derive treatments that are individualized for patients. Ultimately, personalization of health interventions, whether they are with small molecule drugs or cell-based therapies, rests on a firm understanding of the mechanisms of person to person variations in treatment outcomes. Solid research into the basic science and biology behind stem cells must be performed before scientists leap into the clinical trials. The heterogeneity among patient factors and the biology of different stem cell types merits the need for personalized approach to stem cell therapy and other cell-based treatments. With sound scientific research in the diverse genetic and cellular profiles among patients, prospects on tailored treatment employing stem cells holds promising potential. Scientists should soon prepare to discover methods by which the therapeutic potentials of stem cell therapy can be harnessed, and clinicians should be prepared to employ these novel strategies to particular subsets of patients.

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ABBREVIATIONS

ESCs	Embryonic stem cells
GvHD	Graft-versus-host disease
HSCs	Hematopoietic stem cells
IFN- β	Interferon- β
IFN- γ	Interferon- γ
IL-1 α	Interleukin-1 α
IL-1 β	Interleukin-1 β
MSCs	Mesenchymal stem cells
NK	Natural killer cell
Th1	T-helper 1
Th2	T-helper 2
TNF- α	Tumor necrosis factor- α

T_{regs} Regulatory T cells

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Fig. (1).

Pharmacogenomics and host factors influencing effectiveness of stem cell therapy. These factors include, but are not limited to, differences in host genetic make up, age and health of patients, local inflammation at target sites, overall immune status, and past medical history. The diversity of factors that can theoretically determine outcomes of stem cell clinical trials warrants multi- and inter-disciplinary approaches, with particular attention to personalized medicine.

Table 1**Immunomodulation by Mesenchymal Stem Cells**

Property	Implications	Reference
Veto-like effects as third party cells	Suppression of mixed lymphocyte reaction; facilitation of engraftment	[20]
Altered antigen presenting cell maturation	Modulation of T cell responsiveness and inhibitory cytokine (IL-10) production	[100]
Regulatory T cell induction	Promotion of graft survival upon pre-transplantation with MSCs	[23]
Suppression of dendritic cell maturation from monocytes	Modulation of antigen presentation and graft tolerance	[101,102]
Prevention of B cell differentiation and maturation	Reduction in IgM, IgG, IgA production and inhibition of humoral response	[103]
Inhibition of cytotoxic T cell development	Reduced cell-mediated response	[104]
Bimodal immune response to IFN- γ	Variation in antigen presentation depending on cytokine milieu	[10]
Toll-like receptor expression	Control of MSC migration and immunomodulation	[105]
Polarization towards T-helper 2 response	Reduction in anti-tumor activity from T-helper 1 response	[11]

Shown above are the known immunological phenomena regulated by mesenchymal stem cells (MSCs). The majority of immunological evidence demonstrates a suppressive effect for MSCs in both cell-mediated and humoral arms of the immune system. Co-transplantation with, or pre-transplantation of MSCs has implications in the treatment of inflammatory and autoimmune conditions. Although the *in vitro* data (shown in the table) are well supported in the literature, the *in vivo* efficacy remains to be established. Microenvironmental factors must be considered for optimal effects to be observed.

Table 2**Fate Specification of Mesenchymal Stem Cells**

Cell Fate (Differentiation)	Induction Agents	References
Osteogenic	β -glycerophosphate, ascorbic acid-2-phosphate, platelet lysate	[34,37]
Adipogenic	Dexamethasone, isobutylmethylxanthene, indomethacin	[34]
Chondrogenic	TGF- β , BMP-2, BMP-7, collagen-based hydrogels	[106]
Stroma	Horse serum, hydrocortisone, 2-ME	[70]
Cell Fate (Transdifferentiation)	Induction Agents	
Neuronal	bFGF, retinoic acid	[15,16]
Dopaminergic	bFGF, FGF8, SHH	[36]
Cardiac	5-azacytidine	[45]
Hepatic-like	HGF, DMSO, OSM	[73]

Shown above are the representative inductive agents to differentiate and transdifferentiate MSCs into specialized cells. Shown also are the examples of transdifferentiation, thus challenging the multipotential designation of MSCs.

Abbreviations: bFGF, basic fibroblast growth factor; FGF, fibroblast growth factor, SHH, sonic hedgehog, TGF- β , transforming growth factor- β , BMP, bone morphogenetic protein; DMSO, dimethyl sulfoxide; HGF, hepatocyte growth factor; OSM, oncostatin M; 2-ME, 2-mercaptoethanol.