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Review

Therapeutic Mesenchymal Stromal Cells for Immunotherapy and for Gene and Drug Delivery

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Mesenchymal stromal cells (MSCs) possess several fairly unique properties that, when combined, make them ideally suited for cellular-based immunotherapy and as vehicles for gene and drug delivery for a wide range of diseases and disorders. Key among these are: (1) their relative ease of isolation from a variety of tissues; (2) the ability to be expanded in culture without a loss of functionality, a property that varies to some degree with tissue source; (3) they are relatively immune-inert, perhaps obviating the need for precise donor/recipient matching; (4) they possess potent immunomodulatory functions that can be tailored by so-called licensing *in vitro* and *in vivo*; (5) the efficiency with which they can be modified with viral-based vectors; and (6) their almost uncanny ability to selectively home to damaged tissues, tumors, and metastases following systemic administration. In this review, we summarize the latest research in the immunological properties of MSCs, their use as immunomodulatory/anti-inflammatory agents, methods for licensing MSCs to customize their immunological profile, and their use as vehicles for transferring both therapeutic genes in genetic disease and drugs and genes designed to destroy tumor cells.

Mesenchymal Stromal Cells (MSCs): Discovery, Origin, and Basic Biology

The existence of non-hematopoietic stem cells within the bone marrow (BM) was first postulated in 1867 by the German pathologist Julius Cohnheim, who made the remarkable demonstration that the BM gives rise to circulating cells, including stromal cells, and that these cells can then migrate to sites of injury and inflammation within the body, exit the bloodstream, enter the affected tissue, and participate in the process of wound healing, a rather controversial notion at the time, and even to this day.[1–4] It would be nearly 100 years from this remarkable discovery before Tavassoli and Crosby[5] would provide further evidence for the existence of these non-hematopoietic stem cells by showing that transplanting intact pieces of BM into extramedullary sites in rodents not only reconstituted hematopoiesis, but also led to the formation of structures reminiscent of the native BM, and that Herzog and Bucala[6] would put forth the idea of circulating "fibrocytes."

Despite the existence in the literature of these seminal studies, however, Friedenstein is generally credited with the definitive discovery of marrow stromal/stem cells, as a result of a series of publications in the 1970s. In these reports, Friedenstein et al.[7] performed elegant studies demonstrating that the BM contained a plastic-adherent fibroblastoid cell subpopulation that possessed colony-forming potential, had the ability to differentiate into osteoblasts *in vitro*, and was capable of transferring the hematopoietic microenvironment to ectopic sites following transplantation, thereby establishing the concept that the marrow microenvironment resided within the so-called stromal cells of the BM. It was not until 1991, however, that Simmons and Torok-Storb[8] developed the Stro-1 antibody to identify these cells and that Caplan[9] attributed properties of true stem cells to MSCs. This finding led him to coin the term "mesenchymal stem cell," which he defined as "stromal cells that are capable of differentiating through a series of separate and unique lineage transitions into a variety of end-stage phenotypes."[9] This far-sighted hypothesis was provided with solid scientific support a few years later, when the first detailed description of the trilineage potential of MSCs was published.[10]

Since these ground-breaking studies, great strides have been made in both our understanding of these cells and their potential therapeutic uses.[11] MSCs are now known to be a key part of the highly specialized BM microenvironment/niche that maintains hematopoietic stem/progenitor cells (HSCs) and regulates hematopoiesis.[4,12–14] MSCs actively participate in maintaining the critical balance between self-renewal and differentiation of HSCs via both direct cell-cell interactions and by secreting cytokines to exert paracrine effects.[15,16] Despite their essential role within the BM, MSCs are very rare, being present at a frequency of only about 1 in 10,000 nucleated cells shortly after birth and declining thereafter as a function of age.[17] In addition to their role in regulating hematopoiesis, MSCs also serve as progenitors for mesodermal tissues,[10,18–20] giving rise, in the presence of the appropriate stimuli, to bone, cartilage, and fat.[10]

Sources of MSCs and Tissue Repair

Although much work to date has focused on MSCs isolated from adult murine and human BM, it is important to realize that tissue-specific MSCs, or pericytes, are now known to be widely distributed in perivascular regions of almost all tissues throughout the body, where they are thought to play an important role in tissue homeostasis, physiological remodeling, injury repair, and tissue regeneration

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throughout the life of the individual.[21–25] Indeed, our group and others have successfully isolated MSCs from numerous tissues, including brain, liver, lung, fetal blood, umbilical cord blood, amniotic fluid, placenta, kidney, and liposuction material.[18,20,26–30] However, even though MSCs from each of these various tissues appear similar with respect to phenotype and overall differentiative potential, differences exist in the protein and transcriptomic profiles, as well as in the secretome and global microRNA (miRNA) expression profile of MSCs, such that each tissue's MSCs possess a molecular fingerprint indicative of their tissue of origin,[24,28,31–37] and we and others have provided experimental evidence that these differences likely reflect differing biological properties/potential *in vitro* and *in vivo*.[38–41]

Based on their widespread distribution and ability to mediate repair in a wide range of injuries and diseases, it is intriguing to speculate that MSCs may in fact represent a latent pool of stem/progenitor cells, distributed ubiquitously throughout the body,[42] potentially capable of migrating to sites of injury/inflammation and generating tissue-specific cells and/or releasing paracrine factors to repair the damage in question.[43] Indeed, MSCs have been proven to have the ability to migrate and seed specifically into damaged tissue sites, where they can replace damaged or diseased cells via differentiation/ reprogramming *in situ*[44–54] (even into cells of endodermal and ectodermal derivation, albeit at low frequencies[55–58]), and to secrete cytokines, proteolytic enzymes, and angiogenic factors that serve to stimulate the proliferation and survival of endogenous cells within the local tissue while inhibiting apoptosis and fibrosis.[44,59–65] Scadden and colleagues[66] provided evidence in a model of type 1 diabetes that MSCs may actually be mobilized from the marrow in response to inflammation, adding further credence to this claim. This ability to reprogram to adopt alternate cellular fates and thereby repair damaged tissue has, however, been questioned by some in the field, as has the ability of these cells to engraft long-term in human recipients.[67] Using a fetal sheep model, our group was the first to show that human MSCs engraft in multiple tissues following *in utero* transplantation, and they possess the ability to reprogram and/or differentiate to give rise to a wide variety of tissue-specific cells in this non-injury setting, in the absence of cellular fusion or donor-to-host mitochondrial/membrane transfer.[55,68] Our work in the fetal sheep model agrees with clinical observations made by Fisk and colleagues,[69,70] who used X-Y fluorescence *in situ* hybridization (FISH) to demonstrate decade-long persistence of MSCs of fetal (male) origin within tissues of the mother. Thus, within the fetal milieu, there is very strong evidence to support the engraftability and broad differentiative potential of MSCs.

Isolation of MSCs

The most straightforward method to obtain MSCs is to exploit their plastic adherence and their ability to be passaged with trypsin. This simple approach yields a relatively morphologically homogeneous population of fibroblastic cells within only two to three culture passages.[10,71,72] However, "MSCs" derived in this way represent a highly heterogeneous population of cells with multiple distinct phenotypic and biological properties, only a small percentage of which are true mesenchymal stem/progenitor cells.[73] In addition, studies have provided evidence for the existence of specific subpopulations, each with its own distinct differentiative preference toward specific lineages, in addition to true MSCs that possess multilineage differentiative potential.[74] This heterogeneity creates a lack of consistency and has confounded comparison of results obtained in different laboratories. To further complicate matters, the conditions used during culture expansion can also exert a marked effect on the phenotype and functionality of the final cell product, as can their cryopreservation.[75–78]

For clinical applications, it is essential to start with a well-defined cell population, including validated functionality. However, unlike the hematopoietic system,[79–82] there is no widely accepted and straightforward *in vivo* assay to quantify the stemness/multipotency of MSCs, making it difficult to convincingly distinguish primitive MSCs from progenitors and more differentiated stromal elements.[83] Bianco et al.[67] and Keating[84] developed a model in which MSC potency could be assayed by transplanting a clonal population of MSCs and assessing the formation of an ectopic marrow niche that could support hematopoiesis *in vivo*, but this system has not seen widespread use in the field. To overcome the lack of a simple *in vivo* readout for potency, ever-increasing numbers of studies have used surface markers in an effort to identify antigens that are unique to MSCs, thereby allowing their isolation to relative purity, and to catalog specific subsets of MSCs with respect to proliferation and survival rates, immunomodulatory features, and their differentiation bias.[3,74] These efforts to define an MSC-specific marker have, however, thus far been largely unsuccessful;[83] while a diverse range of antigens have been found to be expressed on the surface of MSCs, including CD29, CD44, CD54 (intercellular adhesion molecule 1 [ICAM-1]), CD73, CD90, CD105, CD106 (vascular cell adhesion molecule 1 [VCAM-1]), and Stro-1,[18,20,74,83,85–88] none of these has proven to be unique to these cells. Due to this lack of unique markers, and in an effort to achieve comparable and unambiguous results with respect to MSC functionality and efficacy between various groups, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy (ISCT) proposed a minimal set of standard criteria to be used to define human MSCs,[11,18,20,89] and these are still considered the reference/benchmark for characterizing these cells at the end of their *in vitro* expansion. These criteria include: (1) plastic adherence; (2) expression of CD105, CD73, and CD90; (3) the absence of the hematopoietic markers CD45, CD34, CD11b, CD14, CD19, CD79a, and histocompatibility leukocyte antigen-DR isotype (HLA-DR); and (4) the ability to differentiate into chondrocytes, osteoblasts, and adipocytes *in vitro*, when provided with the appropriate stimuli.[18,74,90] In addition, the absence of CD31 (platelet endothelial cell adhesion molecule [PECAM]) is also considered to be important, to exclude confusion with phenotypically very similar endothelial cells. Recently, efforts have been undertaken to establish monitoring of CD142/tissue factor, as both a phenotypic marker and safety criterion for MSC products, as MSCs expressing high levels of this molecule can trigger the instant blood-mediated inflammatory reaction (IBMIR), leading to rapid elimination of the infused cells and loss of therapeutic effect.[77,91]

A critical caveat to this set of ISCT standards, however, is that these criteria are based on the features of MSCs that have been culture-expanded *in vitro*, and they may not accurately reflect the properties that MSCs possess *in vivo* within the BM and other tissues. Moreover, it is important to realize that even MSCs that meet the above minimal criteria often represent a mixture of cells with diverse phenotypes, biological activities, and corresponding therapeutic potential,[74,92,93] and that these properties can be dramatically altered by cryopreservation, negatively affecting therapeutic outcome.[77,78,91] For example, the expression of molecules such as CXC chemokine receptor (CXCR)4, platelet-derived growth factor (PDGF) receptor, and VCAM-1 that play a vital role in MSC biology/function have been shown to be restricted to specific subsets of MSCs.[94–96] Selecting for the fraction of MSCs that express CXCR4, or forced overexpression of CXCR4, led to a marked enhancement in tissue repair in multiple injury models, including myocardial infarction,[97] stroke,[98,99] acute kidney injury,[100] and early liver regeneration,[101] as well as augmented homing to the BM.[99,100] Likewise, the subpopulation of MSCs expressing high levels of the Stro-1 antigen was shown to possess high growth capacity and enhanced trafficking and tissue repair abilities. These studies led to Stro-1 being proposed as a critical marker to assess MSC functional potency.[55,102–105] Studies have reported similar findings for subsets of MSCs expressing CD105, CD106, CD146, and CD271.[95,106–122]

Collectively, these studies provide compelling evidence that it may be possible to develop far more effective therapies by using specific subpopulations of MSCs that exhibit an enhanced ability to provide the function most appropriate for the condition to be treated.

Immunological Properties of MSCs and Their Use to Modulate Immunity

MSCs are fairly unique cells from an immunological standpoint, in that they express only HLA-I antigens on their surface, but lack expression of HLA-II and the co-stimulatory molecules CD80 and CD86 that are required for T lymphocyte activation.[84,123–128] As a result, MSCs are not very good targets for lysis by cytotoxic T cells, nor do they efficiently induce the proliferation of allogeneic lymphocytes when used as stimulators in a traditional mixed lymphocyte reaction. These properties led to the general consensus that MSCs enjoy a relatively immune-inert status *in vivo*, a premise that is supported by an accumulating body of evidence showing that MSCs can be transplanted across allogeneic barriers without eliciting a robust immune response.[129–135] Note, however, that this important issue is still the subject of intense investigation,[130–136] as rodent transplantation studies have indicated that allogeneic MSCs can, in fact, elicit an immune response *in vivo*,[90] inducing allospecific $CD4^+$ and $CD8^+$ memory T cells[137,138] and the formation of alloantibodies.[132,139,140] Similarly, we and others have shown that human MSCs can, under certain conditions, serve as effective targets for lysis by natural killer (NK) cells.[141–144] This is clearly an area that merits further study, as the true immune status of allogeneic MSCs is obviously of critical importance for their safe (and effective) clinical use.

In addition to their interesting "hypoimmune" nature, a wealth of data has now provided irrefutable proof that MSCs have highly potent immunomodulatory/immune-dampening properties both *in vitro* and *in vivo*.[84,125,145–148] Since Bartholomew et al.[149] showed in 2002 that MSCs had the ability to suppress a mixed lymphocyte response *in vitro* and prevent rejection in a baboon skin allograft model *in vivo*, countless studies have shown that MSCs can act upon both the innate and adaptive arms of the immune system and target virtually all immune cells, impairing the proliferation and/or functionality of T, B, and NK cells in response to mitogens, alloantigens, and activating antibodies, both *in vitro* and *in vivo*.[60–62,83,86,123,124,145,149–159] These effects appear to be mediated both by direct contact with target cells[160–162] and by the release of myriad soluble molecules.[127,163–169] These findings have generated tremendous enthusiasm and hundreds of clinical trials to test their potential as immunotherapeutics to treat diseases involving immune dysregulation, such as autoimmune disorders, inflammatory bowel disease (IBD), type 1 diabetes, type 2 diabetes, arthritis, ischemia-reperfusion injury, and to thwart the immunological complications that arise following the transplantation of HSCs, solid organs, and vascularized composite allografts (VCAs).[90,125,135,143,170–197]

Of particular clinical interest, MSCs also exhibit a remarkably potent ability to skew the balance between effector/memory T cells and $CD4^+FoxP3^+$ regulatory T cells (Tregs), polarizing both naive and memory T cells toward a Treg phenotype *in vitro* and tipping the alloimmune response toward tolerance and long-term allograft acceptance *in vivo*.[90,125,145,149,156,160,198–201]

MSCs can also induce the formation of non-traditional $CD8^+$ Tregs that can act to suppress allogeneic lymphocyte proliferation[86,156,202,203] and stimulate the differentiation of B cells into regulatory B cells (Bregs), which further aid the process of tolerance induction.[204] In addition to their effects on regulatory T and B cell populations, MSCs also efficiently target and modulate memory T cells, potently suppressing the *in vitro* proliferation of human memory T cells in response to alloantigens or cytokines[205–207] and the proliferation and cytotoxic function of memory T cells against alloantigens of both minor and major histocompatibility complexes *in vivo* in mice.[125,205,208]

MSCs also exert marked suppressive effects on antigen-presenting cells (APCs). Looking specifically at the "professional" APCs, dendritic cells (DCs), co-culture with MSCs has been shown to affect DC maturation, differentiation, and functionality with respect to antigen presentation.[146,209] Specifically, when in the presence of MSCs, DCs were unable to respond to maturation signals and failed to upregulate expression of HLA-DR, CD80, and CD86.[209–213] Moreover, the presence of MSCs resulted in a shift in the cytokine profile of the DCs such that the levels of the inflammatory cytokines tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and interleukin (IL)-12 were all decreased, while expression of the anti-inflammatory cytokine IL-10 was upregulated.[150,209] As a result of these alterations, MSC-exposed DCs were no longer able to activate effector T cells, but instead

stimulated the proliferation of Tregs. Under particular conditions, MSCs have also been shown to skew the inflammatory phenotype of macrophages (another APC) by converting pro-inflammatory M1-type cells into a more anti-inflammatory M2-type subset, adding yet another layer of complexity to their immunomodulatory repertoire.[214–216]

The mechanisms by which MSCs exert these varied effects on multiple immune effector lineages are not at all straightforward, and a wide range of molecules/pathways have been implicated. Some of the major players in this ever-growing list include: transforming growth factor (TGF)-β1, hepatocyte growth factor (HGF), prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), inducible nitric oxide synthase (iNOS), leukemia inhibitory factor (LIF), HLA-G, heme oxygenase-1 (HO-1), insulin growth factor (IGF), IGF-binding protein (IGFBP),[217] TNF-stimulated gene 6 (TSG-6), IL-10, the semaphorins (in particular semaphorin-3a[218,219]), the galectins (specifically Gal-1, Gal-3, and Gal-9[219–223]), erythropoietin-producing hepatocellular (Eph) receptor tyrosine kinase-B/Eph family receptor-interacting protein (ephrin)-B, glycoprotein A repetitions predominant (GARP; a receptor for latent TGF-β), and even purinergic signaling.[59–62,124,161,224–243]

Of particular interest in this long list are three molecules/pathways that were initially discovered for their role in promoting maternal tolerance to the fetus which, immunologically speaking, represents a haplo-identical allograft during pregnancy. The first of these is IDO, the enzyme that catalyzes the rate-limiting step in the pathway that breaks down tryptophan into kynurenine. IDO is now recognized to mediate immunosuppression and to play a key role in the generation of immune tolerance in many settings aside from pregnancy,[244] primarily via inducing the generation of Tregs and tolerogenic DCs.[182,245] The IDO pathway represents one of the main mechanisms by human MSCs mediate immunosuppression.[246] This is in marked contrast to murine MSCs, which work primarily through iNOS, and rat MSCs, which work through HO-1.[246–248] These key species differences highlight the care that must be taken when performing studies with MSCs in rodents and trying to directly extrapolate the findings to the human setting. To further complicate matters, the mechanism by which human MSCs exert their immunomodulatory effects has also been demonstrated to depend on the tissue from which the MSCs are derived. MSCs from the BM and umbilical blood suppressed T cells by inducing cell cycle arrest, while MSCs from adipose tissue and umbilical cord inhibited T cell proliferation by inducing apoptosis.[249]

Interestingly, Chen et al.[250] found that dexamethasone inhibits the expression of iNOS in mouse MSCs and IDO in human MSCs, and thereby abolishes the immunomodulatory and therapeutic effects of MSCs from both species. This finding is of great clinical importance, as it suggests that concurrent treatment of patients with steroids would likely interfere with any therapeutic effects that would be mediated by infused MSCs. It also provides a possible explanation for why the outcomes of studies using MSCs in similar disease settings have often been contradictory.

HLA-G is another molecule that was initially described for its involvement in fetal-maternal tolerance and is now recognized for its ability to affect the function of diverse immune cell populations and to induce several subsets of suppressive/regulatory cells.[251] Specifically, HLA-G is thought to regulate the cytokine balance by polarizing the T helper (Th)1/Th2 balance in favor of Th2 with increased IL-10 secretion.[252] While subpopulations of MSCs express both the membrane-bound (HLA-G1) and soluble (HLA-G5) forms of HLA-G, Giuliani et al.[253] provided evidence that it is the surface expression of the HLA-G1 isoform that is responsible for the T cell inhibition by MSCs. Siegel et al.[254] made the significant observation that both HLA-G1 and HLA-G5 are downregulated by MSCs during culture expansion, underscoring the importance of using MSCs at relatively low passage number if one wishes to maximize their immunomodulatory properties. We and others have shown that the immunosuppressive effects of human MSCs can be enhanced by engineering them to stably produce HLA-G1 via lentiviral transduction.[255,256] Quite intriguingly, when other vector systems were used to deliver the HLA-G1 gene, its immunomodulatory benefits were lost.[256] In lieu of genetic modification, one can imagine that by selecting a subpopulation of MSCs that express high levels of HLA-G1, it should be possible to ensure that potent immunosuppressive effects are achieved upon infusion.[235]

The third molecule that MSCs have co-opted from fetomaternal tolerance during pregnancy is LIF.[257–259] MSCs express high levels of LIF,[260,261] and these levels increase during co-culture with lymphocytes. Data from Najar et al.[262] and Nasef et al.[263] have demonstrated that LIF has the ability both to induce direct inhibition of effector T cells and to promote the generation of Tregs, thereby playing a pivotal role in MSC immunomodulation. Subsequent studies have indicated that LIF likely exerts these immune-dampening effects, at least in part, through its ability to modulate HLA-G production by MSCs.[264]

In an effort to make sense of this complex array of immunoregulatory pathways, Nasef et al.[265] recently proposed two distinct mechanisms by which MSCs can tip the balance in favor of T cell tolerance. The first of these relies on the induction of the tolerogenic genes IDO, LIF, and HLA-G, and it takes place in a contact-independent manner. The second mechanism requires direct contact between the MSCs and the target T cells, and it involves the modulation of IL-10 and TGF-β gene expression within the T cells.

Decrypting how all of these MSC-derived regulatory mediators act in concert with one another will make it possible to better define the regulatory network by which MSCs tune the immune microenvironment and provide fundamental information for developing more clinically effective MSC-based immunotherapies. It is quite likely that our current imperfect knowledge of MSC immunobiology can explain why the results of clinical trials to date have been inconsistent and why conclusive proof of efficacy often remains elusive.[146,152,246,266,267]

To aid the reader in navigating the myriad factors and many effects that MSCs exert on the immune system and the range of

Table 1. Immunomodulatory Effects, Mechanisms, and Therapeutic Uses of MSCs

MSCs	Representative References
Effect	
Suppress mixed lymphocyte reaction (MLR)	149
Impair proliferation and/or functionality of:	
T cells	123,124,149,150,152,205–208
B cells	158,159
NK cells	153
DCs	146,151,157,209–213
Skew the balance of T cells toward FoxP3$^+$ Tregs	90,125,145,149,155,156,160,198–201
Induce formation of non-traditional CD8$^+$ Tregs	86,156,202,203
Stimulate Bregs	204
Skew macrophages toward an anti-inflammatory M2 phenotype	214–216
Soluble Factor Produced by MSCs to Modulate Immunity	
TGFb1	265
HGF	167
PGE2	165
IDO (human)	244,246,267
iNOS (mouse)	162,164
HO (rat)	239,267
LIF	261–263
HLA-G	253–256
IGF/IGFBP	217
TSG-6	266
IL-10	265
Semaphorins	218,219
Galectins	161,219–223
Ephrin B	230
GARP	228
Adenosine	224,225
Disease/Therapeutic Target	
Inflammatory bowel disease (IBD)	3
Type 1 and type 2 diabetes	177,314–318
Arthritis	180
Ischemia/reperfusion injury	96,100
To thwart immune response to transplanted:	
HSCs	109,129
Solid organs	90,149,176,181,182
Vascularized composite allografts (VCAs)	126,171,172,183

immune-related therapeutic targets being considered, a summary appears in Table 1, including citations of salient studies.

Tailoring the Immunomodulatory Properties of MSCs

DCs and macrophages serve as conventional immunocompetent "tissue sentinels," but evidence is increasing to suggest that MSCs also participate in the process of immunosurveillance.[248] It is critical to realize that MSCs are not static and they do not constitutively express all of their myriad immunomodulatory functions discussed in the preceding section. Rather, MSCs can actively sense the surrounding microenvironment and modulate, accordingly, the function of various immune cells within the host, dependent upon the prevailing immunological milieu.[268,269] The surrounding microenvironment can influence the immunologic phenotype and immunomodulatory behavior of MSCs.[270] When presented with inflammatory stimuli, such as the proinflammatory cytokines TNF-α and INF-γ, MSCs are induced to adopt an immunosuppressive phenotype. Conversely, when inflammation is absent, MSCs tend to exist in a proinflammatory state.[269,270] This ability to adapt to their local surroundings has led some to describe MSCs as "environmentally responsive therapeutics."[4,269,271] Indeed, for MSCs to exert their multiple therapeutic effects, the communication of MSCs with the environment upon arrival to the injured site is essential.

Interestingly, to produce optimal immunomodulation, MSCs require priming with a combination of pro-inflammatory cytokines, specifically IFN-γ together with either TNF-α or IL-1.[272] In response to this priming, MSCs switch their secretome toward an anti-inflammatory and pro-trophic phenotype, producing high levels of immunoregulatory factors, cell-mobilization factors, and growth factors that work together to facilitate tissue repair by resident cells.[11,270,273–275] Priming of MSCs with the pro-inflammatory cytokines IFN-γ and TNF-α also induces upregulation of chemokine receptors such as CXCR3 and CC chemokine receptor 5 (CCR5),[276] enabling these primed MSCs to sense the chemoattractant gradient and more efficiently home to sites of injury,[277] and the adhesion molecules ICAM-1 and VCAM-1, which potentiates the accumulation of immune cells in close proximity to MSCs, thereby enhancing their immunosuppressive effects.[162,278]

One must exercise great care, however, when attempting to augment the immunomodulatory properties of MSCs by priming them with pro-inflammatory cytokines, as data indicate that the concentration and duration of exposure to a given cytokine can dramatically influence the biological response of MSCs,[270] with rapid intense exposure of MSCs to high concentrations of pro-inflammatory cytokines producing a very different response compared to prolonged exposure at lower concentrations.[279–281] For example, the effect of IFN-γ on MSC expression of HLA-DR is bimodal. HLA-DR expression is induced at low IFN-γ concentrations, inducing MSCs to adopt a pro-inflammatory phenotype that enables them to uptake, process, and present soluble exogenous antigens through their major histocompatibility complex (MHC) class II molecules, leading to the activation of naive CD4$^+$ T cells and induction of CD8$^+$ T cells *in vitro* and

in vivo.[86,136,282–292] In contrast, HLA-DR expression is downregulated at high IFN-γ levels, thereby stripping MSCs of their ability to act as APCs and triggering a tolerogenic phenotype.[282,285,287,293,294]

Sivanathan et al.[295] showed that IL-17A priming of MSCs may represent a novel immunomodulatory strategy and an alternative to IFN-γ to enhance the immunosuppressive properties of MSCs while maintaining their native immune-inert state. MSCs primed with IL-17, unlike those primed with IFN-γ, showed no induction or upregulation of MHC class I, MHC class II, or of the T cell costimulatory molecule CD40 that could have the potential to negatively affect their fate/survival *in vivo*.

Mimicking infection *in vitro* using agonists to activate specific Toll-like receptors (TLRs) has also been shown to modulate the functions and responses of MSCs.[4,296,297] This should not be surprising, since the activation of TLRs expressed on the surface of MSCs by their corresponding ligands present at the site of tissue injury/inflammation is thought to be one of the major factors influencing the biological functionality of MSCs *in vivo*.[298] In humans, 10 functional TLRs have been described.[299] These receptors are expressed on immune cells and non-immune cells such as MSCs.[297] In nature, TLRs are activated by pathogen-associated molecular patterns (PAMPs), which are derived from microbial structures[300], released by normal cells in response to ischemia, tissue damage, and trauma. The TLRs are traditionally divided into two subgroups depending on their subcellular localization and the nature of the PAMP ligands they sense. TLRs 1, 2, 4, 5, 6, and 10 are expressed at the cell surface and recognize microbial membrane components, while TLRs 3, 7, 8, and 9 are expressed only in intracellular membrane compartments (endoplasmic reticulum, lysosomes, and endosomes) and recognize viral nucleic acids. In human MSCs, expression of many of these TLRs has been shown to be dependent on their tissue of origin, and to be markedly altered by environmental conditions such as inflammation.[290,296,301–307] Indeed, many of the immunomodulatory properties MSCs exhibit following cytokine priming can be recapitulated by adding agonists to specific TLRs.[290] Importantly, activation of TLRs on MSCs does not induce the expression of HLA-I, HLA-II, CD80, or CD86, and, consequently, TLRs do not alter the immunogenicity of MSCs.[302,308,309]

Waterman et al.[310] reported a new paradigm for MSC immunomodulatory functions by showing that they can be specifically polarized by downstream TLR signaling, analogous to that described for the monocyte/macrophage lineage. They showed that MSCs primed with the TLR4 agonist lipopolysaccharide (LPS) adopted a pro-inflammatory phenotype (MSC1), and they produced mediators such as macrophage-inflammatory protein (MIP)-1α and MIP-1β, regulated on activation, normal T cell expressed and secreted (RANTES), CXC chemokine ligand (CXCL)9, and CXCL10 that are able to induce T lymphocyte activation. In contrast, MSCs primed with the TLR3 agonist poly(I:C) adopted an immunosuppressive/tolerogenic phenotype (MSC2), expressing factors known to play a key role in the T cell-inhibiting effects of MSCs such as IDO, PGE2, NO, TGF-β, HGF, and HO-1. Giuliani et al.[311] furthered these studies by showing that exposure to certain TLR ligands can modulate the surface expression and secretion of MICA (MHC class I polypeptide-related sequence A) by primed MSCs, which can protect primed MSCs against activated NK cells and inhibit cytolytic functions of NK cells. In other related work, Lombardo et al.[302] showed that activation of TLRs 2, 3, 4, and 9 on human adipose-derived (hAD)-MSCs induced molecules in the nuclear factor κB (NF-κβ) pathway, including manganese superoxide dismutase (MnSOD), and that expression of MnSOD provided better engraftment and induced the survival of hAD-MSCs in inflammatory conditions or injured tissues.

These collective findings led Waterman et al.[292] to propose that MSCs should be skewed toward the desired MSC1 or MSC2 phenotype prior to infusion in order to ensure that they produce the desired immune actions. However, things may not be as neat and simple as they appear with this new paradigm, as the molecular mechanisms underlying MSC polarization into these two distinct phenotypes remain unclear, as do the effects of TLR-priming MSCs on T lymphocyte functions.[303,306,308,310] Moreover, studies by other groups have suggested that the time of exposure to TLR ligands and the concomitant presence of other cytokines are likely to add layers of complexity to this regulatory pathway.[248]

MSCs as Antigen-Specific Immunotherapies

Broad-based non-specific immunosuppression is far from optimal for treating autoimmune diseases and other disorders that involve immune dysregulation due to the unacceptably high toxicity and risk of opportunistic infection. MSCs have been tested for their ability to modulate adaptive immunity non-specifically,[312–316] but if it were possible to exploit the marked immunomodulatory effects of MSCs with their ability to serve as unconventional APCs upon activation/priming,[136,282–285] MSCs could theoretically become an antigen-specific therapy,[317] a holy grail in the field of immunotherapy.[318] van Megen et al.[317] provided *in vitro* evidence that peptide-pulsed activated human MSCs can inhibit antigen-specific responses, thus taking a critical step toward the clinical translation of MSCs as an adaptive, antigen-specific immunotherapy for treating autoimmunity. Interesting, HLA class II matching with the recipient was found to be required to deliver adaptive immune alterations, implying that the suppressive licensing by MSCs is a direct consequence of peptide presentation on the appropriate HLA restriction elements to the T cell. However, matching the MSCs for one HLA haplotype with the T cell donor was sufficient for antigen-specific inhibition, increasing the number of recipients who could potentially be treated with a given off-the-shelf MSC-based product.[136] Intriguingly, the authors also found that while activation and peptide-pulsing of human MSCs resulted in inhibition of T cells, performing the same procedure with mouse MSCs resulted in the activation of T cells,[285] again underscoring the species-specific differences that exist between the MSCs of mice and humans with respect to their immunomodulatory properties and the importance of using an appropriate model when aiming to translate research findings to the clinic.

MSCs as Vehicles for Gene Delivery

MSCs possess tremendous therapeutic potential due to their ability to home to sites of injury within the body, mediate potent immunomodulation to restore homeostasis, and both give rise to tissue-specific cells and release trophic factors that trigger the tissue's own endogenous repair pathways.[43,55,68,166] However, these properties are just the beginning of the therapeutic applications for MSCs.[319–321] By using gene transfer to engineer MSCs, it is possible to either augment their innate production of specific desired proteins or to enable them to express proteins they normally do not, and it is possible to greatly broaden the clinical utility of MSCs. MSCs possess several qualities that make them ideal vehicles for gene delivery.[43,55,63,68,71,150,322] First, they can be transduced at high efficiency with all of the major viral-based vectors, including adeno-associated virus (AAV),[323,324] adenovirus,[325–327] lentiviruses,[328–333] and the murine retroviruses,[327,334–337] and robustly produce a wide range of cytoplasmic, membrane-bound, and secreted proteins. Following transduction, the gene-modified MSCs can be selected and extensively expanded *in vitro* to generate adequate numbers for transplantation. This is in marked contrast to other cells being used as gene delivery vehicles, such as HSCs, which cannot be expanded *in vitro* without loss of *in vivo* functionality. The immune-inert nature of MSCs (as discussed in detail in preceding sections) also represents a significant strength, as it may enable MSCs expressing a "foreign" protein to go undetected by the recipient's immune system, and the use of allogeneic "off-the-shelf" gene-modified MSCs should be possible. In our opinion, these features combine to make MSCs one of the most promising populations for use in cell-based approaches to gene therapy.

Despite their many advantages as gene delivery vehicles, however, few studies have thus far explored the potential of using gene-modified MSCs to treat genetic diseases. One disease that we and others have spent many years investigating with regard to the potential of MSCs as cellular vehicles for delivering a therapeutic gene is hemophilia A.[338–344] Both hemophilia A and B are rather unique genetic diseases, because the missing coagulation factor (FVIII or FIX, respectively) does not need to be expressed in either a cell- or tissue-specific manner to produce phenotypic correction. The endothelial cells of the liver sinusoids are thought to be the primary natural site of FVIII synthesis.[345] However, expression of FVIII in other tissues exerts no deleterious effects, as is evidenced by low levels of endogenous expression of FVIII in multiple tissues throughout the body.[343,346–348] To be therapeutic, FVIII simply has to be expressed in cells with ready access to the circulation, so that it can be secreted into the bloodstream and exert its appropriate clotting activity. Hemophilia A is also unique in that very low levels of FVIII are actually required to exert a pronounced therapeutic benefit. Levels of FVIII of only 2%–3% of normal would convert a hemophilia A patient from a severe, life-threatening phenotype to a moderate phenotype, greatly improving their quality of life.

FVIII is a challenging protein to express, as it is large and needs to undergo complex post-translational modifications to fold properly and exert procoagulant activity. As such, forced overexpression of FVIII can often place an undue amount of stress on the endoplasmic reticulum and trigger the unfolded protein response (UPR).[349,350] We previously showed that MSCs/pericytes form various tissues of the body endogenously produce and secrete fully functional FVIII, albeit at low levels,[343] thus establishing that these cells possess the requisite machinery to express, process, and secrete FVIII. In support of this supposition, we and others have also shown that MSCs can be transduced with FVIII-expressing viral vectors and secrete high levels of FVIII protein[339,340,342,351] that has a specific activity, relative electrophoretic mobility, and proteolytic activation pattern that is virtually identical to that of FVIII produced by commercial cell lines.[340]

Given the widespread distribution and engraftment of MSCs following systemic infusion, their ability to efficiently process and secrete high amounts of biologically active FVIII, and their documented ability to migrate to sites of injury and inflammation within the body, we performed a pilot study evaluating the ability of haploidentical (paternal) BM-derived MSCs transduced with a lentiviral vector driving constitutive expression of FVIII to correct two pediatric sheep with severe hemophilia A[342,352]. At the time of MSC administration (via ultrasound-guided intraperitoneal injection), both animals had received multiple infusions of human FVIII protein to treat spontaneous bleeding events, they had low-titer inhibitors to FVIII, and the rapidly progressing hemarthroses of their legs had rendered them nearly immobile. Within days following the infusion of FVIII-expressing MSCs, the hemarthroses resolved, both sheep regained the ability to stand, and they subsequently returned to normal levels of activity/movement. All spontaneous bleeding events also ceased.

At roughly 6 months after MSC infusion, the animals were euthanized and their tissues collected for analysis. The haploidentical FVIII-expressing MSCs were found in almost all tissues examined but were present in the highest numbers in the joints that had been bleeding at the time of infusion. These findings illustrate several key aspects that support the value of MSCs as vehicles for gene delivery. The first of these is the fact that the haploidentical MSCs were able to engraft and persist in this large animal model system following postnatal infusion, supporting the assertion that MSCs are indeed relatively immune-inert and can be transplanted across allogeneic barriers. The second finding of note is that the MSCs that were infused into the peritoneal cavity migrated to and engrafted predominantly in the joints with active bleeds, establishing that MSCs can sense and are drawn to the injury and inflammation present in the context of hemarthroses. The third and perhaps most remarkable observation is the cessation of bleeding and the resolution of the hemarthroses in animals who both had inhibitors to FVIII. This finding supports our assertion that the immune-inert nature of MSCs can be exploited to deliver an immunogenic transgene and achieve durable expression without rejection of the transgene-expressing cells. It also suggests that FVIII-expressing MSCs could potentially serve as a novel immune-evading treatment for hemophilia A patients with inhibitors.

These promising results in the context of hemophilia A provide a critical proof of principle that MSCs can be used as vehicles to deliver therapeutic gene products to numerous tissues in the body, and that this approach could thus provide a permanent cure for a diverse range of diseases.

MSCs for Cancer Immunotherapy

Cancer represents a condition in which there is a state of chronic inflammation and the forming tumor creates a selective need for new cells, much as occurs during development or following injury. A wealth of data now supports the extraordinary ability of MSCs to "sense" this need and migrate to the forming tumor following intravenous administration, likely due to the inflammatory mediators present at the site of a tumor.[353–359] Once they arrive at the tumor, however, MSCs appear to integrate and contribute to the newly forming supportive "stroma" of the tumor.[59–62,359–364] This property constitutes a serious risk, since infused MSCs could actually provide support, contribute to the growing tumor, and dampen tumor immunity through their immunomodulatory properties.[192,361,362] Clearly, these are not desirable outcomes in the clinical treatment of cancer. However, this tumor-homing propensity could be harnessed to achieve a powerful and unique means of selectively delivering chemotherapeutics, cytokines, and the genes for drug-activating enzymes to tumor cells *in vivo*.[359,364–370]

At the present time, the utility of many of the most promising biological agents for cancer therapy is limited by their short *in vivo* half-life and the pronounced toxicity as a result of their inability to distinguish between tumor cells and all of the normal, non-malignant cells within the body. Given their ability to selectively migrate to the tumor site, using MSCs to deliver these cancer therapeutics could solve both problems, as the MSCs would ensure the therapeutic/toxic payload is only unloaded within the tumor. This should greatly increase the intratumoral concentration of the agent, boosting its therapeutic effects while simultaneously lowering systemic toxicity.[371,372]

The tumor-homing abilities of MSCs are not limited to solid tumors and the primary tumor mass. On the contrary, studies have now shown that this tumor affinity of MSCs also confers them with the ability to actively seek out metastases, even when they are located at sites far removed from the primary tumor.[322,364,373,374] Given the difficulty and poor clinical outcomes that are often achieved using traditional approaches such as surgery and radiotherapy/chemotherapy to treat tumors that are highly invasive or prone to metastasis, this property of MSCs holds great potential for tackling these difficult malignancies.[364]

Looking first at the use of MSCs to deliver chemotherapeutics directly to the tumor, an extensive body of work has demonstrated that human and mouse MSCs have the ability to take up chemotherapeutics such as paclitaxel and gemcitabine.[375–379] Interestingly, these highly toxic agents had little effect on the viability, migration, cell cycle, or differentiation potential of MSCs,[380] enabling them to be used as "Trojan horses,"[381] to selectively deliver chemotherapeutic agents to tumors *in vivo*, to then act, in effect, as tumor-resident pharmacologic pumps.[382] While this approach was successful, more recent work has shown that the efficiency of uptake and the resultant therapeutic efficacy can be greatly enhanced if the chemotherapy drugs are first loaded into nanoparticles (NPs) which are then taken up by the MSCs, creating so-called "nanoengineered MSCs."[383] When MSCs were nanoengineered to carry paclitaxel and infused intravenously in an orthotopic human lung tumor model, they selectively homed to the tumor sites, where they were retained, thereby creating cellular drug depots that released the drug over an extended time period.[380,383,384] This was in marked contrast to free paclitaxel-loaded NPs, which predominantly accumulated in the liver and spleen following intravenous injection. Importantly, the use of the nanoengineered MSCs led to more effective inhibition of tumor growth and superior survival than did either standard solution or NP-encapsulated forms of paclitaxel, despite significantly lower total doses of paclitaxel being used. The ability to greatly lower the dose administered also mitigated the common toxic side effects of paclitaxel such as leukopenia, greatly improving safety and tolerability. Collectively, these studies provided compelling evidence to support the clinical utility of MSCs as delivery vehicles for chemotherapeutic agents.

The first MSC-based gene therapy for cancer began roughly 17 years ago when human MSCs were engineered to express IFN-β in an effort to activate the antigen-presenting properties of MSCs and thereby induce an immune response to the tumor. This approach was shown to enable successful targeted delivery of this potent immune-stimulating agent to orthotopic tumors in metastatic breast and melanoma cancer models.[359,364] IFN-β-transduced MSCs significantly inhibited tumor growth in severe combined immunodeficiency (SCID) mouse xenograft models of human melanoma and established MDA-231 or A375SM pulmonary metastases, and the survival of animals was prolonged,[359] while the intravenous infusion of recombinant IFN-β produced minimal benefits in this same model.

Similar highly promising results were obtained[385] with human MSCs engineered to express and secrete IFN-γ, one of the most important molecules in suppressing cancer development and progression.[386] Despite the positive effects of IFN-γ on cancer cells, systemic administration is associated with significant side effects, including nausea, depression, fever, and leukopenia.[387] As with the studies using IFN-β-transduced MSCs,[359,364] the engineered MSCs delivered IFN-γ locally into the tumor, thereby eliminating systemic toxicities and activating the innate immune system, which decreased tumor growth and increased overall survival in a challenging model of neuroblastoma, characterized by liver and lung metastases.

TNF-related apoptosis-inducing ligand (TRAIL/CD253) is another cytokine whose gene has been inserted into MSCs to treat and eliminate tumors.[363,373,374,388] TRAIL can have potent anti-cancer effects, because it induces apoptosis in cells that express the death receptors TRAIL-R1 and TRAIL-R2, but not the decoy receptors TRAIL-R3 or TRAIL-R4. Since many tumor cells express the TRAIL death receptors in the absence of the decoy receptors, they are highly vulnerable

to TRAIL-induced apoptosis.[389] Quite fortuitously, MSCs express very low levels of the TRAIL death receptors and normal levels of the decoy receptors. As such, TRAIL-transduced MSCs are resistant to TRAIL-induced apoptosis and can thus continuously deliver TRAIL to tumor cells *in vivo*. Indeed, human BM-MSCs that were virally transduced to overexpress TRAIL exhibited potent antitumor effects when tested in murine orthotopic tumor models.[366]

Gene-directed enzyme prodrug therapy (GDEPT), or suicide gene therapy, is another approach to cancer treatment in which MSCs have featured prominently for several years. GDEPT is a two-step process. In the first step, one transfers a gene encoding a prodrug-activating enzyme to the tumor, ideally in a selective fashion. In the second step, an inactive prodrug is systemically administered, but is only activated into cytotoxic metabolites locally within the tumor cells expressing this enzyme.[390–392] To maximize the benefit of this approach, it is essential that the cytotoxic metabolites are able to diffuse through the cell membrane, since expression of the transgene does not occur in all tumor cells. This so-called "bystander" effect results in the death of not only the tumor cells in which the metabolites are formed but also the neighboring tumor cells that do not express the transgene.[393] In addition to this direct effect of the toxic metabolites, the dying tumor cells can induce a host immune response mediated by NK cells, T cells, and macrophages, accompanied by increased levels of various cytokines, further enhancing the therapeutic effects of GDEPT.[394–397]

Two of the most common prodrug-activating enzyme and prodrug combinations employed thus far include:

(1) The thymidine kinase gene from herpes simplex virus (HSV-TK) combined with ganciclovir (GCV).[398,399] GCV is a nontoxic purine analog that HSV-TK phosphorylates to a monophosphate form.[400] Host cell kinases then complete the conversion to the active triphosphate form, which inhibits DNA synthesis, leading to induction of apoptosis.
(2) The cytosine deaminase (CD) gene from *E. coli* combined with 5-fluorocytosine (5-FC).[401–406] CD catalyzes the hydrolytic deamination of the non-toxic 5-FC molecule into 5-fluorouracil (5-FU), which is then transformed within cells into other cytotoxic metabolites that are incorporated into DNA and RNA, leading to cell cycle arrest and apoptosis.[407]

Both of these combinations have been tested successfully *in vitro* and preclinically in animals bearing a variety of human tumors, and these studies have shown that the active triphosphate form of GCV and 5-FU both diffuse freely across cell membranes to exert a strong bystander effect.[408–419] Unfortunately, however, the therapeutic success of this approach has been fairly limited, largely due to lack of specificity and low efficiency of direct gene delivery to the tumor cells *in vivo*.[420,421]

To overcome these issues, investigators have turned to MSCs to achieve the promise of GDEPT.[422,423] MSCs can be transduced at high efficiency *in vitro* with viral vectors encoding the prodrug-activating enzyme. Upon intravenous infusion, the engineered MSCs home to the target tumor, the inactive prodrug is administered systemically, and the tumor-resident MSCs activate the prodrug to its cytotoxic metabolites, which are then pumped out into the local microenvironment killing neighboring tumor cells.[390,391,424,425] A number of *in vitro* and *in vivo* studies have demonstrated the efficacy and potency of this MSC-based approach to cancer immunotherapy against a wide variety of human tumors.[382,423,426–434]

Perhaps the most recent and innovative approach to using MSCs as cancer immunotherapeutics has arisen in the field of bispecific antibodies (bsAbs).[435] A number of studies have demonstrated that primary human T cells engaged with bsAbs can drive a profound anti-tumor reaction, both *in vitro* and *in vivo*.[436,437] However, to sustain clinically relevant plasma levels, continuous delivery of bsAbs is necessary, due to their short half-lives *in vivo* and the rapidity with which they are cleared from the circulation.[438,439] Using MSCs as cellular bsAb production factories would enable the continuous production and secretion of bsAbs continuously in the patient's body.[322,440] Studies exploring this tactic have demonstrated that gene-modified MSCs are able to express a CD33-CD3 specific bsAb at high levels and mediate efficient lysis of acute myelogenous leukemia (AML) blasts by human primary T cells of both healthy donors and AML patients. While still relatively early in development, these initial studies highlight the vast potential of combining bsAb with MSCs to achieve potent anti-tumor effects.

Concluding Remarks

Since their initial identification as cells contributing to the hematopoietic niche within the BM, MSCs have received an ever-increasing amount of attention, mainly for reasons completely independent of their hematopoiesis-supporting properties. There are currently more than 800 human trials listed on ClinicalTrials.gov that employ MSCs for regenerative medicine and as modulators of the immune system.[77,441] By virtue of the fact that their surrounding milieu can "license" MSCs, it is possible to tailor these cells to either inhibit or to stimulate an immune response, making them a unique and valuable tool in the immunotherapy arsenal. This remarkable immunological plasticity enables MSCs to be used to dampen aberrant immune responses in autoimmune disease, help to prevent rejection following solid organ or hematopoietic cell transplantation, deliver highly immunogenic therapeutic transgene products such as FVIII for treating genetic diseases, and to selectively target tumor cells for immune elimination. It is truly an exciting time in the MSC field, with each month seeing new and highly promising therapeutic uses for these versatile cells. We envision that the coming years will see the immunomodulatory properties of MSCs forming the basis for mainline therapy for a wide range of inherited and acquired disorders, enabling the successful treatment, and perhaps cure, of many diseases and forms of cancer for which current therapeutic strategies are ineffective.

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