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Mesenchymal Stem Cells as Immunomodulators in Transplantation

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1. Introduction

In recent years it has become evident that mesenchymal stem cells (MSCs), also termed mesenchymal stromal cells, have potent immunomodulatory effects in addition to their known ability of organ regeneration and recruitment to sites of injured or inflamed tissue (Caplan 1991; Garin, Chu et al. 2007; Nauta and Fibbe 2007; Bianco, Robey et al. 2008; Shi, Hu et al. 2010). While the ability of MSCs to mediate tissue and organ repair replacing damaged tissue has initially been attributed to their multilineage differentiation potential, it is now widely attributed to their ability to home to site of injury secreting cytokines and growth factors that mediate the repair process inducing proliferation and differentiation of progenitor cells (Karp and Leng Teo 2009; Hoogduijn, Popp et al. 2010; Sordi, Melzi et al. 2010). Whether MSCs migrate from the bone marrow in case of injury or if the stem cell niche available in the diseased organ replaces dying cells remains to be elucidated.

MSCs have been demonstrated to exhibit a profound immunomodulatory effect on T cells, B cells, and Natural Killer (NK) cells. This effect has been recently shown to be mediated via soluble factors, and this can be enhanced further if direct cell–cell contact between the MSCs and immune cells is allowed (Ren, Zhao et al. 2010). Via these factors, MSCs inhibit T cell proliferation (Di Nicola, Carlo-Stella et al. 2002; Aggarwal and Pittenger 2005), maturation and differentiation of B cells (Corcione, Benvenuto et al. 2006; Tabera, Perez-Simon et al. 2008; Asari, Itakura et al. 2009), maturation of dendritic cells (DCs) (Nauta, Kruisselbrink et al. 2006), generation of cytotoxic T cells (Angoulvant, Clerc et al. 2004) and proliferation and cytotoxic activity of NK cells (Rasmusson, Ringden et al. 2003; Sotiropoulou, Perez et al. 2006; Spaggiari, Capobianco et al. 2008), while inducing regulatory T cells (Tregs) (Prevosto, Zancolli et al. 2007; Di Ianni, Del Papa et al. 2008; Crop, Baan et al. 2010).

MSCs have been shown to induce immunologic peripheral tolerance, suggesting their potential application in a therapeutic approach for immune mediated disorders. In this context, MSCs can be used to support the function of standard pharmacological immunosuppressants to reduce their dosage or even replace such toxic immunosuppressants promoting long-term survival of the transplanted organ (Crop, Baan et al. 2009).

Limited information is available about the molecular mechanisms responsible for the immunomodulation By MSCs and there is no single mechanism responsible for their observed tolerogenic effect. However, MSCs have been considered to potentially work through multiple mechanisms and have the ability to affect immunological, inflammatory and regenerative pathways supporting or replacing current pharmacological agents.

Considering their immunosuppressive properties in addition to their low inherent immunogenicity (Rasmusson, Uhlin et al. 2007) makes MSCs an attractive treatment option in cell and organ transplantation potentially improving the graft outcome and eliminating a long immunosuppressive treatment regimen (Ryan, Barry et al. 2005; Eggenhofer, Steinmann et al. 2011). Both the immunosuppressive effects of MSCs and their regenerative potential participate to facilitate grafting of a transplanted organ as well as repair and regeneration of the organ after transplantation.

In both allogeneic hematopoietic stem cell transplantation (AHSCT) and organ transplantation setting, major problems exist due to the lack of suitable donors. High histo-incompatability between donor and recipient is often associated with an increased risk of graft rejection or graft versus host disease which MSCs might ameliorate if infusion of MSCs along with the organ transplant increases organ engraftment making this immunoprivilege useful for transplantation. Indeed, in one of the first in vivo studies showing the advantageous immunosuppressive effect of MSCs, allogeneic MSCs were demonstrated to prolong (MHC)-mismatched skin allograft survival in baboons (Bartholomew, Sturgeon et al. 2002).

Furthermore, the immunosuppressive properties of MSCs, in addition to their low immunogenicity features, have prompted researchers to investigate co-transplantation of these cells in AHSCT setting to promote hematopoietic stem cells (HSCs) engraftment and to prevent graft versus host reactions as well as host versus graft reactivity. Additionally, MSCs provide support for the growth and development of HSCs further promoting engraftment. In this, MSCs were shown to interact with HSCs through production of growth factors that influence HSCs-homing and –differentiation (Krampera, Cosmi et al. 2006). This effect was attributed via either cell-cell contact or production of soluble factors by MSCs such as the CXCL12 chemokine which may attract HSCs through its interaction with the CXCR4 ligand (Krampera, Cosmi et al. 2006) hence improving HSCs engraftment.

First clinical trials have been undertaken to assess the safety of MSCs administration as well as a potential treatment option for graft versus host disease (GvHD). Encouraging results have been obtained in patients with steroid resistant GvHD and in the management of chronic GvHD after AHSCT. Interestingly, MSCs treatment improved the overall outcome and successfully attenuated GvHD in these patients (Le Blanc, Rasmusson et al. 2004; Ringden and Le Blanc 2011).

MSCs were shown to attenuate graft rejection and in combination with immunosuppressive therapy were able to prolong cardiac allograft survival when co-administered with immunosuppressive therapy. Indeed, they promote donor-specific graft tolerance and ameliorate the alloimmune response where the use of low dose therapy alone was not sufficient to maintain the graft; only combination therapy with MSCs maintained the cardio graft (Ge, Jiang et al. 2009).

MSCs have also been suggested as a promising cell immunotherapy tool to promote tolerance for organ transplants and to control allograft rejection in post-transplant therapy

settings facilitating both transplant acceptance and physiologic functions (Crop, Baan et al. 2009; Dahlke, Hoogduijn et al. 2009). MSCs have also been recently shown to have an ameliorating effect in a model of acute lung injury were transplantation of MSCs resulted in a significant increase in the level of protective/immunomodulatory Tregs (Sun, Han et al. 2011). Finally, clinical trials are ongoing to determine the efficacy of MSCs as an effective tool for the treatment of autoimmune diseases, such as multiple sclerosis, inflammatory bowel diseases, rheumatoid arthritis, and type 1 diabetes.

2. The biology and originality of mesenchymal stem cells and their generation and expansion in vitro for therapeutic use

MSCs are a self-renewing heterogeneous population of multipotent cells, originally isolated from bone marrow as shown in pioneer experiments by Friedenstein and colleagues and first referred to as colony-forming unit fibroblasts (Friedenstein, Chailakhyan et al. 1974). Since then, MSCs have been isolated from many other adult tissues such a umbilical cord blood, placenta, amniotic fluid, peripheral blood, adipose tissue and various other somatic tissues sharing the regenerative as well as the immunomodulatory properties of MSCs (In 't Anker, Scherjon et al. 2004; Zuk 2010; Bianco 2011) but have mainly been characterized after isolation from bone marrow.

MSCs can be expanded in vitro as plastic adherent cells with a fibroblast-like morphology and can be differentiated into cells of mesodermal lineage (osteocytes, chondrocytes and adipocytes) (Pittenger, Mackay et al. 1999) as well as cells from other embryonic lineages (Sanchez-Ramos 2006; Schwartz, Brick et al. 2008). At present, MSCs lack a definitive marker and no single marker has been identified distinguishing MSCs however the International Society for Stem Cell Research has outlined minimal criteria to characterize human MSCs, these cells have been reported to be positive for CD73, CD90, CD105 and major histocompatibility complex class I (HLA-ABC). They are devoid of the hematopoietic markers such as CD14, CD 19, CD34, CD45 and for major histocompatibility complex class II, (HLA-DR) (Dominici, Le Blanc et al. 2006).

An attractive characteristic of MSCs is that they can be easily expanded maintaining a relatively stable phenotype and karyotype along with their potential to differentiate into multiple mesodermal tissues. The possibility that MSCs might undergo malignant transformation does exist, however this might be directly linked to the origin of the tissue. Interestingly, it has been shown that human bone marrow derived MSCs could be expanded in vitro and despite decreased proliferative capacity upon prolonged expansion and eventual cell senescence, no chromosomal abnormalities were detected rendering these cells suitable for cell therapeutic approaches (Bernardo, Zaffaroni et al. 2007).

However, there is a general consensus that MSCs should be used at low passages when applied in cell therapy as chromosomal modifications and loss of function can occur after prolonged in vitro expansion.

3. The Immunomodulatory properties of mesenchymal stem cells and their role in transplantation

Understanding the mechanisms by which MSCs exert their immunomodulatory effects will have profound therapeutic implications in designing new therapies that can lead to more efficient use of these cells in novel treatment regimens. Currently, there is no single clear

mechanism which clearly clarifies the immunomodulatory effect of MSCs and several mechanisms which sometimes seem paradoxical, have been suggested. Several in vitro experimental studies have shown that the immunosuppressive effect of MSCs is sustained in transwell experiments suggesting that soluble factors are responsible for such inhibition (Di Nicola, Carlo-Stella et al. 2002; Meisel, Zibert et al. 2004; Aggarwal and Pittenger 2005; Gao, Wu et al. 2008; Ren, Zhang et al. 2008; Selmani, Naji et al. 2008), while other studies have claimed a required cell-cell contact which may be due to the use of different systems and cells by the individual research groups (Quaedackers, Baan et al. 2009; Ren, Zhao et al. 2010).

MSCs have been shown to modulate the immune response mainly by inhibiting the proliferation of effector immune cells preventing further damage to injured tissue allowing repair after injury (Uccelli, Moretta et al. 2008). Moreover, MSCs can stimulate the activation and proliferation of Tregs which in turn have a beneficial immunosuppressive effect (Crop, Baan et al. 2010).

When MSCs home to site of tissue inflammation or injury, they release various growth factors which enhance repair at site of defect including : fibroblast growth factor, epidermal growth factor, platelet-derived growth factor, transforming growth factor-β, vascular endothelial growth factor and insulin-like growth factor (Ng, Boucher et al. 2008). MSCs mediated inhibition of effector T cell proliferation seems to be dependent on the microenvironment. In this respect, the presence of pro-inflammatory cytokines such as IFN-γ activates MSCs and this was more effective for the treatment of GvHD (Polchert, Sobinsky et al. 2008). Indeed, it has been shown, that the immunosuppressive capacity of MSCs was enhanced strongly under inflammatory conditions while their differentiation capacity was preserved and suggested that in vitro preconditioning provides MSCs with improved properties for immediate clinical immune therapy (Crop, Baan et al. 2010).

MSCs have been shown to affect almost all cell types of the immune system. It has been demonstrated that MSCs can alter the cytokine secretion profile of immune cells such as decreasing TNF-α and IFN-γ secretion and increasing the secretion of suppressive cytokines (IL-4 and IL-10) and this shift from a pro-inflammatory to a beneficial anti-inflammatory response is of therapeutic advantage for the management of GvHD (Dahlke, Hoogduijn et al. 2009; Hoogduijn, Popp et al. 2010). Moreover, several studies have demonstrated that the MSCs immunoregulatory properties are partially mediated by transforming growth factor (TGF-β), prostaglandin E2 (PGE2), hepatocyte growth factor (HGF) and Indoleamine 2, 3-dioxgenase (IDO) secreted by MSCs in addition to their induction and activation of Tregs all of which can lead to amplification of an effective immunosuppressive response (English, Ryan et al. 2009; Kim, Wee et al. 2011).

3.1 MSC–soluble factors and immunosuppression induction

Different studies have attributed the immunosuppressive effect of MSCs to several immunosuppressive factors leading to different mechanisms of immune cell inhibition. These include, IDO (Meisel, Zibert et al. 2004; DelaRosa, Lombardo et al. 2009), PGE2 (Aggarwal and Pittenger 2005), TGF-β and HGF (Di Nicola, Carlo-Stella et al. 2002), HLA-G (Selmani, Naji et al. 2008), nitric oxide (Ren, Zhang et al. 2008), interleukin (IL)-10 (Gao, Wu et al. 2008) and haeme oxygenase-1 (Chabannes, Hill et al. 2007). One important mechanism is that MSCs suppression is mediated by IDO, a tryptophan catabolising enzyme (Meisel, Zibert et al. 2004). In this, activated T cells or NK cells produce elevated levels of IFN-γ

which in turn stimulates MSCs to produce IDO. IDO metabolizes tryptophan to kynurenine leading to essential tryptophan depletion and accumulation of metabolites in the medium which in turn inhibits proliferation of activated T cells and NK cells (Meisel, Zibert et al. 2004). Competitive inhibition of IDO activity did not completely abrogate MSC mediated immunosuppression and inhibition of IFN-γ was required for complete abrogation (Krampera, Cosmi et al. 2006; DelaRosa, Lombardo et al. 2009). This suggests that co-administration of MSCs with graft T cells-derived IFN-γ activates the immunomodulatory properties of MSCs. Furthermore, there is a species variation in the immunosuppressive mechanisms mediated by MSCs. It has been shown that while human IDO is a major effector molecule for MSCs immunosuppression, mouse MSCs mediate their inhibitory effect of immune responses via nitric oxide playing a central role in such immunosuppression (Sato, Ozaki et al. 2007; Ren, Zhang et al. 2008).

3.2 MSC-immune cell interaction and immunosuppression induction

MSCs have been demonstrated to exhibit a profound immunomodulatory effect on Tregs, cytotoxic and T helper cells, NK cells, B cells and dendritic cells.

3.2.1 Regulatory T cells

Tregs are a subset of T cells that regulate the immune response by suppressing the proliferation and cytokine production of effector T cells. Tregs are thus important for protecting our body by suppressing auto-reactive T cells (Thornton and Shevach 1998; Ng, Duggan et al. 2001). Tregs were shown to be upregulated in the presence of MSCs suggesting that MSCs constitute a suitable niche for Tregs (Crop, Baan et al. 2010). MSCs have been suggested to play a role in Tregs recruitment, regulating and maintaining the T regulatory phenotype and function over time (Prevosto, Zancolli et al. 2007; Di Ianni, Del Papa et al. 2008). Tregs induction has been suggested to be mediated by PGE2, synthesized by cyclooxygenase enzymes (COX) which are expressed by MSCs (Le Blanc and Ringden 2007). Furthermore, Treg induction has been shown to be mediated by direct cell-cell contact between MSCs and $CD4^+$ T cells and the presence of soluble MSC derived factors such as TGF-β1 and PGE2 (English, Ryan et al. 2009). In a recent interesting study by (Sundin, D'Arcy et al. 2011) it was demonstrated for the first time that MSCs share features with regulatory T cells , such as the expression of the Tregs specific transcription factor FOXP3 (Yagi, Nomura et al. 2004) at variable levels. However, the MSC immunosuppressive function is not as tightly linked to FOXP3 expression as is the case for Tregs (Sundin, D'Arcy et al. 2011).

3.2.2 Cytotoxic T cells and T helper cells

MSCs were shown to inhibit the proliferation of $CD4^+$ T helper cells (Di Nicola, Carlo-Stella et al. 2002; Aggarwal and Pittenger 2005). In addition to indirect inhibitory factors produced by MCSs such as TGF-β1, HGF, IL-10, IFN-γ and TNF-α, there is evidence that cell-membrane interaction between MCSs and T helper cells (Quaedackers, Baan et al. 2009) via the intracellular adhesion molecule (ICAM-1) or vascular cell adhesion molecule (VCAM-1) play a crucial role in such immunosuppression (Ren, Zhao et al. 2010). MSCs have also been shown to suppress the induction of cytotoxic T cell response to allo-antigens (Angoulvant, Clerc et al. 2004). However, once cytotoxic T cells are activated, MSCs show no inhibitory effect (Rasmusson, Ringden et al. 2003; Le Blanc and Ringden 2007). On the other hand, it is

not clear how helper and cytotoxic T cells affect MSCs development and function. It has been shown that MSCs have a low immunophenotype as they express low levels of HLA class I, no HLA class II, no co-stimulatory molecules such as CD80 and CD86, and therefore do not induce immune responses (Beggs, Lyubimov et al. 2006; Rasmusson, Uhlin et al. 2007). This should make MSCs transplantable across HLA barriers (Le Blanc, Tammik et al. 2003). However, in contrast to these data, there is evidence that MSCs are immunogenic and can induce memory T-cell responses both in animals (Badillo, Beggs et al. 2007) and human studies (Nauta, Westerhuis et al. 2006). Furthermore, it has recently been reported that MSCs are susceptible for lysis by $CD8^+$ cytotoxic T cells (Crop, Korevaar et al. 2011). Designing tools to escape allogeneic MSCs destruction by cytotoxic T cells should render MSCs a promising therapeutic option for transplantation across MHC barriers.

3.2.3 Natural Killer cells

MSCs have been shown to inhibit NK cell proliferation, and cytotoxicity (Sotiropoulou, Perez et al. 2006). It has been demonstrated that MSCs can mediate this inhibitory effect trough inhibition of cytokine production in addition to the central role played by IDO and PGE2 (Spaggiari, Capobianco et al. 2008). Inversely, it has been shown that MSCs are susceptible for lysis by NK cells (Spaggiari, Capobianco et al. 2006; Crop, Korevaar et al. 2011) as MSCs express the activating NK cell-receptor ligands NKG2D and UL16 (Poggi, Prevosto et al. 2007). Moreover, intravenously administered MSCs have been demonstrated to disappear within days after infusion in immunocompetent mice (Popp, Eggenhofer et al. 2008). It is possible that lysis by cytotoxic T cells (and not NK cells) is responsible for the disappearance of the infused MSCs (Eliopoulos, Stagg et al. 2005). The demonstration of tumour engraftment after administration of autologous MSCs in immunodeficient mice (NK cells intact) further strengthens this possibility.

3.2.4 B cells

MSCs have been shown to suppress B cell terminal differentiation (Asari, Itakura et al. 2009) and modulate their function (Corcione, Benvenuto et al. 2006; Tabera, Perez-Simon et al. 2008). Human MSCs were shown to inhibit antibody production induced in vitro by allo-stimulation (Comoli, Ginevri et al. 2008; English, French et al. 2010). They have the ability to regulate Immunoglobulin production by B cells through soluble factors affecting B cells directly or through an indirect MSCs effect by altering the amount of free alloantigen due to the overall suppression of graft damage (Ge, Jiang et al. 2009).

3.2.5 Dendritic cells

MSCs inhibit monocyte maturation into dendritic cells (Jiang, Zhang et al. 2005), the most potent antigen presenting cells, inhibiting their migration to lymph nodes and thereby reducing their ability to activate allo-reactive T cells (Aggarwal and Pittenger 2005). In this, MSCs were shown to reduce secretion of pro-inflammatory cytokines such as IFN-γ, IL-12 and TNF-α by DCs while IL-10, a suppressive cytokine, was increased leading to the inhibition of DCs maturation and the inability to activate allo-reactive T cells resulting in a state of an immunologic tolerance. The inhibitory effect of MSCs on DC differentiation is mainly mediated through cell-cell contact involving activation of the Notch signalling pathway (Li, Paczesny et al. 2008) as well via soluble factors (Nauta, Kruisselbrink et al. 2006). Moreover, PGE2 produced by MSCs following TNF-α or IFN-γ

stimulation blocks differentiation of monocytes into DCs and stimulates macrophages to produce Il-10.

3.3 MSCs-Galectins and immunosuppression induction

Recently, Sioud et al (Sioud, Mobergslien et al. 2010; Sioud 2011)and Gieseke et al (Gieseke, Bohringer et al. 2010) have described another mechanism of MSCs immunosuppression that involves a family of beta galactosidase-binding proteins named Galectins which are involved in immune tolerance (Garin, Chu et al. 2007). It has been demonstrated that Galectin-1, Galectin-3, Galectin-8 and Galectin-9 are constitutively expressed by human bone marrow MSCs with Galectin-1 and Galectin -3 being further secreted and expressed on the outer plasma membrane (Wada and Makino 2001). New evidence has shown the involvement of Galectin-3 as a regulator of MSCs immunosuppression function inhibiting allogeneic T cell proliferation by MSCs (Sioud 2011). This group demonstrated that gene knockdown of Galectin-3 resulted in less immunosuppressive effect on T cell proliferation (Sioud, Mobergslien et al. 2010). Galectins were also shown to regulate the secretion of pro-inflammatory cytokines and promote expansion of IL-10 producing peripheral Tregs (Sioud 2011). Gieseke et al have also reported that galectin-1 is expressed by MSCs and has immunosuppressive activity on both $CD4^+$ and $CD8^+$ T cells (Gieseke, Bohringer et al. 2010).

4. Clinical prospects of mesenchymal stem cells

Currently suggested clinical uses of MSCs include; differentiation and repairing of damaged tissue e.g. in osteogenesis imperfecta, promoting hematopoietic cell engraftment in AHSCT e.g. in leukaemia and their immunosuppressive abilities in autoimmune-induced inflammatory bowel disease, GvHD induced upon allogeneic cell or organ transplantation as well as autoimmune diseases. Treating autoimmunity with MSCs was first investigated for experimental autoimmune encephalomyelitis as a model for multiple sclerosis in preclinical studies followed by collagen-induced arthritis, autoimmune type 1 diabetes, experimental colitis and lupus nephritis (Uccelli and Prockop 2010).

Still, very little is known about the mechanisms underlying the MSCs immunomodulatory effect in vivo and survival of MSCs upon injection and whether they remain present after systemic injection or local transplantation remains unresolved. However, the clinical studies performed so far look encouraging but still the mechanisms as to how the MSCs regulate immune cells in vivo are still missing. Furthermore, direct methods to assess MSCs mobilization and homing in response to injury or inflammation is essential to eventually understand the underlying mechanism (Karp and Leng Teo 2009).

MSCs are immune-privileged and were shown in most studies to 'escape' the immune system and be tolerated when transplanted across MHC barriers engrafting and failing to induce an immune response. It is important to mention that most of these clinical studies have used MSCs from HLA-identical or near identical donors (Le Blanc and Ringden 2007).

It has been reported that AHSCT recipients have specific tolerance, immune-unresponsiveness, directed towards MSCs but not to other cells from the MSC donor (Sundin, Barrett et al. 2009). This suggests that totally HLA mismatched MSCs from one donor can be expanded ex vivo, cryopreserved and used for the treatment of multiple patients. Furthermore, the inability of MSCs to induce donor specific tolerance suggests that

MSCs co-transplantation with a solid organ most probably facilitates engraftment through the immunosuppressive action of MSCs and not by inducing specific tolerance to the transplant (Sundin, D'Arcy et al. 2011).

4.1 Graft versus Host Disease

GvHD occurs in donated organ recipients and patho-physiologically presents itself as damage in skin, mucosa, gastrointestinal tract, the liver, connective tissue and exocrine glands. It is considered chronic when it persists more than 100 days after transplantation and it is distinguished from acute GvHD which often cannot be ameliorated because of a coexistent immunosuppression. It results from the attack of donor own T cells in the graft on recipient tissues after activation by recipient MHC molecules as well as activation of cytotoxic T cells, antigen presenting cells and NK cells. In GvHD the observation of an increased secretion of pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-1, IL-2 and IL-12 suggests that therapeutic approaches to inhibit these cytokines should lead to a decreased severity of GvHD (Aggarwal and Pittenger 2005).

The immunosuppressive effects of MSCs have been evidenced in a successful clinical trial reported by Ringden et al (Ringden and Le Blanc 2011) in patients presented with acute GvHD after AHSCT and resistant to conventional immunosuppressive therapy. This study showed a dramatic improvement after MSCs infusion with acute GvHD disappearing completely in patients with steroid resistant GvHD suggesting that MSCs could be considered as a promising alternative immunosuppressive therapy with improved long term outcome for the treatment of GvHD (Le Blanc, Rasmusson et al. 2004; English, French et al. 2010; Ringden and Le Blanc 2011; Tolar, Villeneuve et al. 2011).

4.2 Type 1 diabetes

MSCs have been suggested as a prospective cell therapy of autoimmune type 1 diabetes known to be associated with an inflammation in the pancreas and degeneration of β cells. In a preclinical study, it has been shown that co-transplantation of bone marrow cells and syngeneic or allogeneic MSCs initiated endogenous pancreatic regeneration and improved blood glucose levels in streptozotocin induced diabetic mice (Ulicna, Danisovic et al. 2009). The success in the treatment was suggested to be due to MSCs aiding in the regeneration of recipient derived pancreatic beta cells, as well as maintaining the β cell reserve through MSC inhibition of T cell-mediated immune responses against the newly formed β cells preventing further cell degeneration (Voltarelli, Couri et al. 2007; Couri and Voltarelli 2009; Ulicna, Danisovic et al. 2009; Sordi, Melzi et al. 2010). Hence, despite of the persisting hostile autoimmune response in the pancreas, when MSCs are applied at an early stage of the disease they potentially protect and allow the endogenous regeneration of the remaining intact β cell reserve.

4.3 Solid organ transplantation

In solid organ transplantation (e.g. liver transplant), rejection of a transplanted organ is typically caused by induction of T cell proliferation and presentation of allo-antigens to naive and memory T cells by antigen presenting cells (both host and donor) leading to activation and differentiation into effector T cells (Popp, Renner et al. 2009). Both the regenerative and immunomodulatory properties of MSCs are of medical importance in organ transplantation studies. MSCs have been shown to home to site of allograft and help

the body accommodate the new organ through immunosuppression or preventing rejection and acquisition of a state of tolerance (English, French et al. 2010). Furthermore, the regenerative properties of MSCs possibly maintain the organ to be transplanted stretching its lifespan in case of delayed transplantation (Hematti 2008; Hoogduijn, Popp et al. 2010).
For MSCs to be used as a sole therapy or as a combination therapy replacing immunosuppressive drugs, reducing the burden on the patient and the risk for long term side effects, further investigation will be needed to fully explain the immunomodulatory properties of MSCs. However, MSCs were shown to increase immunosuppression when co-administered complementing the therapy (Sundin, D'Arcy et al. 2011). In this regard, an interesting animal study of allogeneic heart graft transplantation that MSCs combined with the immunosuppressive drug mycophenolate mofetil (MMF) promoted the elimination of activated T cells in secondary lymphatic organs, delayed antigen presenting cells activation, and protected the graft from cellular infiltration by modulating the endothelium (Eggenhofer, Steinmann et al. 2011).

5. Quality considerations and regulations in MSC based therapy

Clinical use of MSCs for cellular therapeutic approaches will require that the bio-safety of these cells has to be adequately optimised. This requires the absence of chromosomal, functional, and phenotypical alterations in ex vitro expanded MSCs before considering their injection in patients. The safety of these cells has to be guaranteed upon their administration as immunocompromised patients might have an increased risk of tumour induction or the potential risk of stimulating the growth of a previously undetected cancer. The risk of tumorigenicity and genomic instability remains an obstacle for any given stem-cell based therapy product and will have to be adequately assessed prior to approval for human use (Dittmar, Simann et al. 2010). In this respect, the first clinical trials have been undertaken to assess the safety of MSC administration and potential treatment options for GvHD and it has been reported that autologous and allogeneic MSCs are safe to be injected in patients with life threatening acute GvHD not responding to conventional immunosuppressive therapy without acute toxicity and no signs of ectopic tissue formation (Lazarus, Koc et al. 2005).
MSCs administered for therapy might carry viruses (e.g. herpes simplex virus, cytomegalo virus (CMV), Epstein-Barr Virus (EBV)) transmitted from the donor to the host tissue especially when the patient is immunocompromised. Interestingly, MSCs were shown to exert differential effects on alloantigen and virus-specific T cell responses (Karlsson, Samarasinghe et al. 2008). In this regard, it has been reported that despite MSC infusion as a cellular immunotherapy for GvHD, effector functions of virus specific T cells were retained with very little effect on T cell responses to pathogenic CMV and EBV contrasting the strong immunosuppressive effect on allo-reactive T cells suggesting that MSCs to be a promising cellular immunotherapy (Karlsson, Samarasinghe et al. 2008). This is an important advantageous aspect of MSCs therapy especially since after allogeneic organ transplantation; infections are a major cause of morbidity and mortality in immunocompromised patients. Therefore, MSCs can be safely administered without exacerbating their susceptibility to infectious pathogens.
Currently large clinical trials are being carried out in using MSCs for the treatment of autoimmune diseases including diabetes as well as to treat or ameliorate symptoms of GvHD. Further, clinical trials are also testing the MSCs ability to facilitate the prevention of the rejection upon organ transplantation thereby reducing or completely eliminating the

need for immunosuppressive therapies. Reviewing the clinical trials registered by the U.S. National Institutes of Health (NIH) in the United States and around the world (U.S. National Institutes of Health, http://clinicaltrials.gov/), 168 registered studies (with a start date between September 2004 and March 2011) were found upon entering the search criteria mesenchymal + stem + cells including clinical trials in regenerating organs (e.g. bone fractures, diabetic foot and foot ulcer), liver failure, the administration of MSCs for the treatment of type 1 Diabetes Mellitus as well as Type 2, acute GvHD including studies with patients who have failed to respond to steroid therapy (or with steroid resistance) and poor graft function. In addition to these trials, ongoing clinical studies investigating the safety and efficacy of MSCs promoting engraftment of allogeneic hematopoietic stem cells are in hand (Le Blanc, Rasmusson et al. 2004).

The translation into cellular therapies satisfying safety and efficacy criteria by the regulatory authorities will have to ensure the identity, purity, potency, and lack of tumorigenicity. Questions regarding the expansion of MSCs in vitro and the passage at which they are used as well as the culture conditions containing foetal calf serum, optimal dosing, timing and HLA matching still remain to be answered (Le Blanc, Samuelsson et al. 2007; Sundin, Ringden et al. 2007).

Scientists and clinicians should adhere to local, national and international guidelines and regulations that govern transfer of cells into patients. The clinical trial and the eventual cell therapeutic product is assessed and approved by a national regulatory agency, such as the European Medicines Agency (EMA) or the U.S. Food and Drug Administration (FDA).The International Society for Stem Cell Research (ISSCR) has published guidelines for the clinical translation of stem cells emphasising on the scientific, clinical and ethical issues that should be addressed for a responsible translation of basic stem cell research into suitable clinical applications. The guidelines give attention to the main areas of clinical translational stem cell research namely, cell processing and manufacture, the necessity of preclinical studies and clinical research promoting maximum safety and quality of the cells to be used (Hyun, Lindvall et al. 2008).

6. Conclusion

Understanding the immunomodulatory properties of MSCs and possibly identifying genes that regulate MSC inhibitory function, and genes regulating inflammation which play a major role in transplant rejection and inflammatory processes should help in developing applicable MSC based cellular therapies for solid organ transplantation, GvHD and autoimmune diseases.

The currently available data, in vitro and in vivo, suggest that MSCs can be applied in a wide range of clinical approaches, ranging from tissue repair and regeneration, drug or gene delivery to injured tissue, treatment and prevention of GvHD and AHSCT engraftment offering a promising option for treating autoimmune mediated disorders as well as organ transplantation. Administration of MSCs provides novel modalities for the treatment of patients with allograft rejection with fewer side effects than existing immunosuppressive therapies following organ transplantation.

There is an enormous amount of excitement and the scope of possible stem cell based therapies has expanded in the recent years due to rapid advances in stem cell research. But today the range of diseases where stem cell treatments have been shown to be beneficial in responsibly conducted clinical trials is still extremely restricted.

The best defined and most extensively used is hematopoietic stem cell transplantation in blood malignancies and aplastic anaemia. To design safe and effective cellular therapies, the long term effects of MSCs injection will still need to be shown in relevant clinical trials and further studies are needed to optimize cell-dosing, time of injection and the combination with immunosuppressive drugs to confirm both efficacy and safety of this cell therapy, are still needed within the careful regulations of the EMA and FDA.

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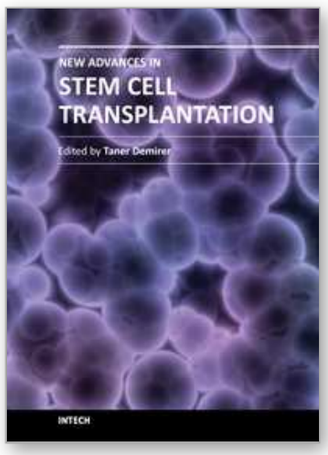

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This book documents the increased number of stem cell-related research, clinical applications, and views for the future. The book covers a wide range of issues in cell-based therapy and regenerative medicine, and includes clinical and preclinical chapters from the respected authors involved with stem cell studies and research from around the world. It complements and extends the basics of stem cell physiology, hematopoietic stem cells, issues related to clinical problems, tissue typing, cryopreservation, dendritic cells, mesenchymal cells, neuroscience, endovascular cells and other tissues. In addition, tissue engineering that employs novel methods with stem cells is explored. Clearly, the continued use of biomedical engineering will depend heavily on stem cells, and this book is well positioned to provide comprehensive coverage of these developments.

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