Clinical Translation of Multipotent Mesenchymal Stromal Cells in Transplantation

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Summary: The prevalence of chronic kidney disease and end-stage renal disease is increasing each year and currently the best therapeutic option for end-stage renal disease patients is kidney transplantation. However, although short-term graft outcomes after transplantation have improved substantially as a result of new and more potent immunosuppressive drugs, the long-term survival has hardly changed. This most likely is caused by a combination of nonimmunologic side effects and sustained alloreactivity to the graft resulting in fibrosis. In addition, current immunosuppressive drugs have side effects, including nephrotoxicity, infections, and malignancies that compromise long-term outcomes. Consequently, there is a strong interest in immunosuppressive therapies that maintain efficacy, while reducing side effects. Because mesenchymal stromal cells have potent anti-inflammatory and antifibrotic properties, these cells are of particular interest as new candidates in transplant recipients. Mesenchymal stromal cells might play roles in the treatment of allograft rejection and fibrosis and in calcineurin minimization and induction protocols. In the present review we discuss both preclinical as well as clinical evidence of their therapeutic potential in kidney transplantation. In addition, challenges and obstacles for clinical translation are discussed.
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Chronic kidney disease (CKD) is a common disease in the Western population because at least 8% of this population has a degree of CKD, placing them at moderate to high risk of developing kidney failure.[1] This figure is increasing each year as a result of an aging population and an increase in the prevalence of chronic (reno)vascular morbidity and diabetes. If the present trend continues, the number of people with CKD will double over the next decade.

Although there are strategies to slow down the progression to end-stage renal disease (ESRD), there are currently no therapies to cure CKD, therefore approximately 5% of patients with diminished kidney function will progress to ESRD with a need for renal replacement therapy.[2] Currently, the best therapy for these patients is kidney transplantation because this improves the life expectancy and quality of life of ESRD patients.

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In patients who have received a transplant, the graft survival rate has increased in the past decades to more than 90%, mainly owing to the reduction of acute rejection within the first year after transplantation. However, long-term graft survival has remained unaltered over the past 2 decades.[3] Both immunologic and nonimmunologic factors contribute to the development of fibrosis in the allograft, including ischemia reperfusion injury, ineffectively or untreated clinical and subclinical rejection, superimposed calcineurin inhibitor nephrotoxicity, and exacerbating pre-existing donor disease. Moreover, long-term systemic immune suppression increasingly is recognized for its numerous side effects, of which infections and malignancies are the most important. Therefore, there is a need for novel treatment strategies to improve both the immunologic acceptance of the graft as well as to prevent fibrosis and foster the regenerative capacity of the transplanted kidney. Mesenchymal stromal cell (MSC)-based therapy has been shown to be a promising candidate for both situations because their properties may influence inflammation and fibrosis.

MSC CHARACTERISTICS

MSCs represent a minor fraction of the bone marrow (0.01%-0.001%). They typically are located perivascularly where they control the vascular bone marrow niche and through differentiation into osteoblasts give rise to the niche for long-term repopulating stem cells.[4] They are isolated easily from the bone marrow because they adhere to plastic and substantially can proliferate and expand in culture.[5,6] Unfortunately, there is no

specific MSC marker and therefore a set of phenotypic and functional criteria were proposed by the International Society of Cellular Therapy (ISCT) including their plastic adherence, tri-lineage differentiation potential, and the expression of the stromal markers CD73, CD90, and CD105 while being negative for the hematopoietic markers CD14, CD34, and CD45.[7] Although several attempts have been made to select a more homogeneous MSC population by using surface markers such as, for example, STRO-1, to date there is no unique marker that allows direct MSC isolation and selection. This may be because MSCs actively interact with surrounding cells through microvesicles and exchange of cell components.[8]

In addition to the bone marrow, perivascular localized MSCs can be found in several, if not all, organs, including the kidney.[9,10] In the mouse, kidney-derived MSCs showed similar marker expression and differentiation potential compared with bone marrow (bm) MSCs; however, when looking at the messenger RNA expression profile and in vivo differentiation potential, these cells appeared strikingly different.[10] These differences may be caused by tissue-specific imprinting during embryogenesis or local cues. This makes kidney- (and other organ-) derived MSCs of particular interest as a new source for renal repair. Bruno et al[11] showed that kidney-derived MSCs can be isolated from human glomeruli as well. Whether there are differences between these MSCs and bmMSCs and whether these differences lead to an improved renal repair mechanism needs to be elucidated further.

The ubiquitous presence of MSCs in tissues probably reflects to a large extent the embryologic development of the structure of tissues and also has initiated the isolation and expansion of MSCs from other tissues for clinical use. These include adipose tissue, umbilical cord, and dental pulp.[12–14] We discuss the advantages and drawbacks of the use of these sources as compared with the use of bmMSCs later.

IMMUNOMODULATORY AND REPARATIVE FUNCTIONS OF MSCS

Because of their perivascular location, MSCs can interact closely with several cell types including endothelial cells, resident macrophages, dendritic cells (DCs), and recruited inflammatory cells (Fig. 1).

The immunomodulatory potential of MSCs is the function studied most extensively. MSCs interact with several key players of both the innate and the adaptive immune system, as extensively reviewed elsewhere.[15,16]

In short, MSCs are able to suppress T-cell proliferation and favor the formation of regulatory T cells (Tregs). In human MSCs, to a large extent this is caused by the secretion of soluble factors including indoleamine

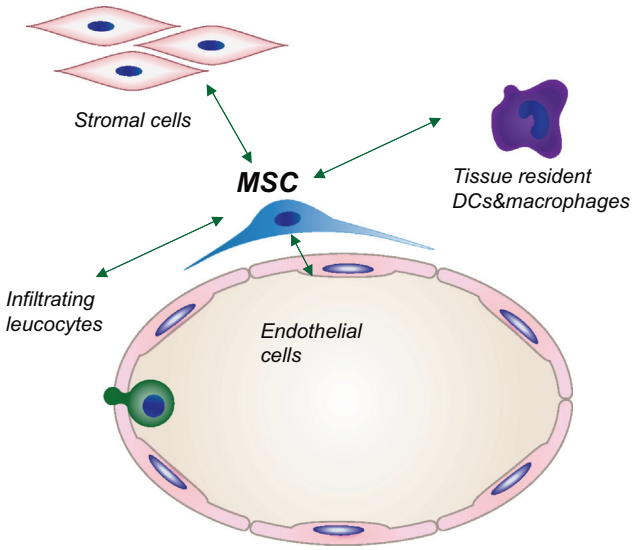

Figure 1. Because of their perivascular location, MSCs have interactions with endothelial cells, stromal cells, tissue resident DCs, macrophages, and infiltrating leukocytes. As a result of all these interactions, they are central in tissue homeostasis.

2,3-dioxygenase (IDO), transforming growth factor-β, and prostaglandin E2 (PGE2).[17–19] With respect to B cells, the effects of MSC therapy is more variable and sometimes even contradictory. In the B-cell–driven disease systemic lupus erythematosus, for example, some studies have shown a beneficial effect of MSC therapy on kidney function, complement depositions, and the levels of circulating double-stranded DNA,[16,20] whereas others did not see an effect on kidney function and survival[21] or even showed a negative effect resulting in increased disease activity.[16,22]

MSCs interact not only with the adaptive immune system but also with components of the innate immune response. MSCs, for example, are able to interfere with DC migration, maturation, and antigen presentation via secretion of interleukin (IL)-6, macrophage colony-stimulating factor (M-CSF), prostaglandin E2, and IL-10.[16] In addition, MSCs also have been shown to modulate natural killer cell responses.[23] These effects of MSCs may recapitulate their function in the bone marrow niches, where one of their main functions is to maintain an inflammatory milieu that allows for progenitor cell maturation and release of blood cells into the circulation.[24] It is also important to realize that part of the regenerative properties of MSCs may depend on their ability to polarize the immune system into a reparative phenotype. For example, M2 macrophages have been identified as tissue-reparative myeloid cells in the kidney by producing a cytokine environment that supports tubular repair and proliferation rather than inflammation.[25] In agreement, genetic or pharmacologic blockade of CSF1 decreases M2 polarization and subsequently inhibits recovery from acute kidney injury.[26]