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ORIGINAL ARTICLE

Role of bone marrow-derived stem cells, renal progenitor cells and stem cell factor in chronic renal allograft nephropathy

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Abbreviations: CAN, chronic allograft nephropathy; HSCs, Hematopoeitic stem cells; MSCs, Mesenchymal stem cells; SCF, stem cells factor; AKI, acute kidney injury; ARF, acute renal failure; CKD, chronic kidney disease; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor; ASMA, alpha smooth muscle actin; IF/TA, interstitial fibrosis/tubular atrophy; CMV, cytomegalo virus; HIV, human immunodeficiency virus; CRP, C-reactive protein; UAE, urinary albumin excretion; UALP, urinary alkaline phosphatase; RI, resistivity index; PI, pulsitility index; RBF, renal blood flow; MoAbs, monoclonal antibodies; PE, phycoerythrin; FITC, fluorescein isothiocyanate.

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KEYWORDS

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Hematopoietic stem cells;
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Renal regeneration

Abstract *Introduction:* Chronic allograft nephropathy (CAN) is a poorly understood clinico-pathological entity associated with chronic allograft loss due to immunologic and non-immunologic causes. It remains the leading cause of late allograft loss. Bone marrow derived stem cells are undifferentiated cells typically characterized by their capacity for self renewal, ability to give rise to multiple differentiated cellular population, including hematopoietic (HSCs) and mesenchymal stem cells (MSCs). Characterization of HSCs includes their multipotency, expression of typical surface markers such as CD34 and CD45, while characterization of MSC includes their multipotency, expression of typical surface markers such as CD90 and CD105, and the absence of hemopoietic lineage markers.
Aim & methods: The aim of the present work was to study the role of bone marrow-derived HSCs and MSCs, renal progenitor cells and SCF in chronic renal allograft nephropathy in relation to renal hemodynamics and histopathological changes. We studied 30 patients with kidney transplantation for more than 6 months, divided into 15 patients with stable serum creatinine and 15 patients who developed CAN. Detection of HSCs and MSCs in the peripheral blood using flow cytometry via detection of CD34, CD45, CD117 and CD106, as well as immunohistochemical detection of CD34, CD133, VEGF and αSMA in transplanted kidney biopsies of patients with CAN were done.
Results: There was a significant increase in the levels of SCF, number of peripheral blood HSCs and MSCs in both transplanted patient groups than the controls and they were higher in patients of group Ia than patients of group Ib, ($F = 39.73$, $P < 0.001$), ($F = 13.28$, $P < 0.001$), ($F = 11.94$, $P < 0.001$), respectively and this was accompanied by evident expression of markers of renal repair.
Conclusion: Stem cells might have a role in renal regeneration in CAN and this may pave the way toward the use of stem cells in correction of CAN.

1. Introduction

Chronic allograft dysfunction (CAD) is a clinico-pathological entity associated with chronic allograft loss caused by immunologic and non-immunologic causes.[1]

Chronic allograft injury is the leading cause of late graft loss after kidney transplantation[2] characterized by progressive interstitial fibrosis and tubular atrophy (IF/TA) as well as microvascular and glomerular damage accompanied by declining graft function months to years after transplantation.[3]

In spite that the incidence of acute rejection and early graft failure had declined dramatically as a result of development in immunosuppressive medications and protocols, and the one year graft survival is now close to 90% in most transplant centers, yet, late allograft failure remains the problem to overcome.[4]

Significant attention has been directed to study the potentiality of stem cells (SCs) in the treatment of a number of acute and chronic diseases.[5,6]

The bone marrow (BM) derived SCs are undifferentiated cells typically characterized by its capacity for self renewal, ability to give rise to multiple differentiated cellular populations (often termed cellular plasticity)[7] and the ability to generate many if not all of the differentiated cell types that are contained in an organ,[8] so that in the presence of damage, these cells can replace the injured ones.[9] The BM harbors two distinct stem cell populations: hematopoietic stem cells (HSCs)[10] and mesenchymal stem cells (MSCs), which provide stromal support for HSCs.[11]

The bone marrow derived HSCs, are pluripotent undifferentiated cells that give rise to all blood cells (erythrocytes, thrombocytes, and leukocytes) and move between the bone marrow and the peripheral blood. The CD34 antigen is highly expressed in pluripotent cells and its expression gradually reduces as the level of maturation of hematopoietic cell lineages increases, to the point of becoming completely absent in fully mature cells. HSCs can be mobilized into the circulation in response to multiple cytokines, chemokines and adhesion molecules.[12,13]

Stem cell factor (SCF), also known as Steel factor or c-kit ligand, is a cytokine produced by stromal cells and is important for mobilization, proliferation and differentiation of HSCs, specifically myeloerythroid lineages. SCF functions by binding to CD117/c-Kit, a tyrosine kinase receptor, highly expressed on HSCs.[14] The SCF/c-Kit signaling pathway promotes cell survival by inhibition of apoptosis in multiple cell types, including HSCs. Interestingly; HPCs express the HSC marker CD34 and SCF and its receptor c-kit.[15]

The other BM derived SCs are the MSCs. MSCs are pluripotent stromal cells which are defined by their plastic adherence, surface marker expression of CD73, CD90, CD105 and CD106 (vascular cell adhesion molecule [VCAM]-1) combined with a lack in expression of hematopoietic markers CD34, CD45, CD14 and HLADR, and the capacity to differentiate into cells of mesodermal lineage including adipocytes, osteocytes, chondrocytes and myocytes.[16]

The MSCs during tissue injury, can be released from their niche in the BM into circulation and recruited to sites of inflammation by migrating toward inflammatory chemokines and cytokines where they differentiate into specialized cells and promote local tissue repair by preventing apoptosis and/or control of inflammation in situ through secretion of growth factors and cytokines and activation of endogenous progenitor cells.[17] MSCs are potent immunomodulators of both the innate and adaptive immune systems.[18] MSCs have been shown to exert a profound inhibitory effect on T cell proliferation and function. MSCs can regulate an innate immune response by signaling dendritic cells to direct an anti-inflammatory T-cell