Editorial

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It is with great pleasure that we publish in this issue of the Journal this contribution of Dr. Federica Casiraghi and Prof. Giuseppe Remuzzi on *Mesenchymal stromal cell-based therapy in kidney diseases and transplantation*.[1]

Regenerative Medicine has made enormous advances in the last few years. Different fields have been involved and the cardiorenal one is certainly of paramount importance.

Research in animal models have brought about very encouraging results and have allowed important pathophysiological insights, while in the clinical field much more work needs to be done.

The attention in this paper is given to mesenchymal cells transplantation. Mesenchymal stromal cells (MSC) are a heterogeneous population of non-hematopoietic cells obtained after *ex-vivo* expansion of adherent cells from bone marrow, adipose tissue, umbilical cord and blood, and other tissues.

These cells in pre-clinical models of kidney disease and transplantation have shown to act on renal and inflammatory cells in multiple, complex and integrated ways, resulting in cell repair and regeneration, inhibition of inflammatory cells and development of cells endowed with their own anti-inflammatory and immune-regulatory properties.

Prof. Remuzzi's contribution is very much in tune with the previously reported results obtained in a pre-clinical setting. Our group has in fact analyzed the impact of mesenchymal stem cells injection (c-Kit selected human amniotic fluid stem cells or rat vascular progenitor cells) in a model of cardiorenal syndrome type II (CRSII) (pulmonary hypertension and right ventricular failure with visceral congestion). We have described the anti-inflammatory effects of cells transplantation, leading to decreased apoptosis, both at kidney and heart level, and modification of the cytokine milieu, ultimately leading to improvement of kidney function and interruption of the vicious cross-talk cycle between kidney and heart.[2,3]

In our study, we have demonstrated that cell therapy with both human amniotic stem cells and vascular stromal cells is able to improve kidney function and restore kidney structure. We have also produced evidence that cell-therapy, by reducing NGAL and its effect on MMP9 at cardiac and kidney levels, could prevent negative remodeling by acting on metalloproteinases thus reinforcing the importance of breaking the vicious cross-talk circle between kidney and heart, which represents a pathophysiological mechanism of function deterioration in CRSII.[2,3]

The hypothesis that we have put forward, and that is enforced also in Remuzzi's paper, is that cell-therapy treatment acts through several mechanisms. Two seem to be particularly important: i) a paracrine mechanism with anti-inflammatory and anti-apoptotic effect; ii) engraftment and differentiation of stem cells with repopulation of tubular, endothelial, SMA and interstitial cells (see Figure 1 on pathophysiology of cardio-renal syndrome and cells repair).[2]

We think that the mechanisms involved in the amelioration of kidney function are complex, comprising the direct effect of engrafted cells in the damaged organ, the paracrine effect of the injected stem cell, the improvement of cardiac and vascular function. The contribution of each factor is at the moment impossible to be weighed. Our data have been also of help for clarifying the paracrine effects exerted by the injected cells, and the conclusions we draw are in line with those outlined by Remuzzi and Casiraghi in their paper.[1]

The encouraging data of our group, together with the others present in the literature, have helped to pave the way for exploring the use of MSC in clinics as innovative therapeutic tools for patients with renal diseases and transplantation.

In this review, Remuzzi and Casiraghi summarize the available results of clinical studies of MSC in pa-

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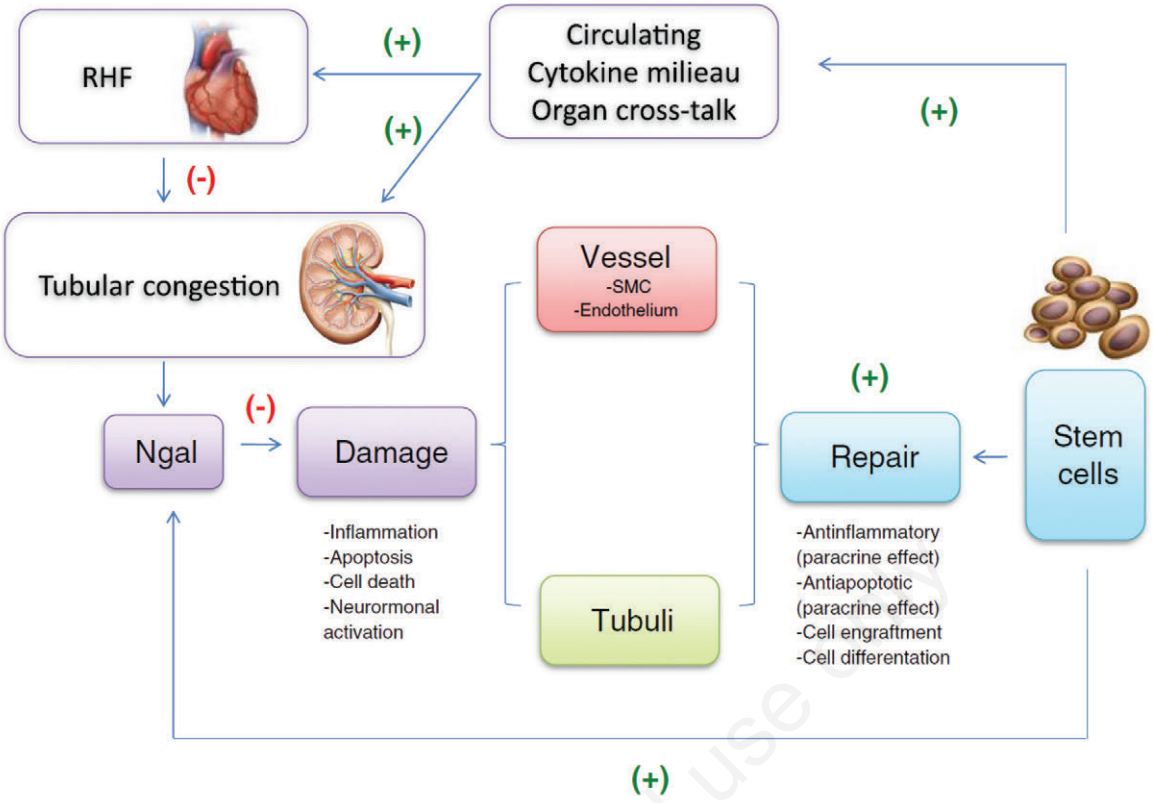

Figure 1. Stem cells mechanisms of injury and repair in cardiorenal syndrome type II cell-therapy is able to: i) produce anti-inflammatory and anti-apoptotic renal effects (paracrine); ii) produce cell engraftment and differentiation with regeneration of vascular and tubular cells; iii) reduce circulating cytokines with effects on organ cross-talk; iv) reduce kidney, circulating and heart NGAL with secondary effects on MMP9 and prevention of negative cardiac remodeling. *Modified from Vescovo* et al.*, 2019.*[2]

tients with post-cardiac surgery, acute kidney injury, chronic kidney diseases - including diabetes, renovascular disease and lupus nephritis - and in kidney transplant recipients, with a particular focus on their experience with MSC therapy as a pro-tolerogenic strategy in kidney transplantation.

They conclude that available studies, mainly phase 1, indicate that MSC therapy is safe and feasible and not associated with adverse events, at least in the short- and mid-term. They make the point that encouraging results have been reported in renovascular disease and kidney transplantation, while the available clinical studies in acute kidney injury and chronic kidney disease (CKD) have contrasting outcomes. This is not the case in our model of CRSII where stem cells have a favorable effect on CKD secondary to heart failure and congestion. There is a gap that still limits the translation of MSC cell therapy into clinical practice but we hope this may be filled in the future putting together the knowledge and the experience gained in the pre-clinical and clinical fields.

References

1. Casiraghi F, Remuzzi G. Mesenchymal stromal cell-based therapy in kidney diseases and transplantation. Ital J Med 2019;13:3-14.
2. Vescovo G, Castellani C, Fedrigo M, et al. Stem cells transplantation positively modulates the heart-kidney cross talk in cardiorenal syndrome type II. Int J Cardiol 2019;275:136-44.
3. Angelini A, Castellani C, Virzì GM, et al. The role of congestion in cardiorenal syndrome type 2: new pathophysiological insights into an experimental model of heart failure. Cardiorenal Med 2015;6:61-72.