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INVITED COMMENTARY

Erectile Dysfunction

Commentary on: "Human umbilical cord Wharton's jelly-derived mesenchymal stem cell transplantation could improve diabetic intracavernosal pressure"

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The article by Wu *et al*.[1] is an interesting and meticulous work investigating the role of human umbilical cord Wharton's jelly-derived mesenchymal stem cells (hWJ-MSCs) in the treatment of erectile dysfunction (ED) in the diabetic rat model.

The pathophysiology of ED is complex and can be caused by several factors including vascular, hormonal, and neural diseases, or can be drug-induced, as well as caused by psychological factors. Diabetes mellitus type 2 (DMT2) is an endocrine disorder that represents a major public health and economic concern with high worldwide prevalence. A common and often underestimated complication of DMT2 is ED. In fact, ED is a reliable indicator of organ-related and vascular complications in DMT2. Besides the standard treatment of ED described also by the European and American guidelines, other promising therapeutic strategies are currently under investigation and the use of stem cells is one of them.

Wu *et al*. transplanted hWJ-MSCs into the corpus cavernosum of streptozotocin-induced diabetic rats and evaluated the erectile function one month later. The investigators noticed a significantly improved intracavernosal pressure by hWJ-MSC treatment and higher VEGF, eNOS, IGF, and bFGF expression levels in the hWJ-MSC injection sites than in the control rats. These results suggest that hWJ-MSC transplantation might alleviate diabetic erectile dysfunction probably through increased production of paracrine growth factors.

Our only concern is the use of human umbilical cord Wharton's jelly-derived mesenchymal stem cells in rats. Historically, these cells do not rise any immunological response in the host. In fact, mesenchymal stem cells (MSCs) lack CD80, CD86, and have extremely low expression of MHC II,[2] and thus do not elicit immunologic reactions mediated by T effector cell. This property that MSCs possess makes them an excellent candidate for allogeneic therapies.[3] However, the use of xenogeneic hWJ-MSC in experimental studies makes difficult the extraction of results that might apply to humans as well. MSCs act in different ways and the paracrine action is only one of them though very important. In the current model, Wu *et al*.[1] could investigate only the paracrine function. That might lead to underestimated results. The use of homologous cells might produce more impressive results and reveal more complex pathways of actions of hWJ-MSC. On the other hand, truth is, several other works using human stem cells in animal models have been published so far. All of them with the same limitation though. The significant beneficial effects that Wu *et al*.[1] demonstrated in their last published work justify their efforts and must give more strength to similar attempts to fully elucidate the role and the biological pathways of action on hWJ-MSC in the penile tissue in diabetic patients.

MSCs under conditions of stress or injury react similarly as that the immune system cells react to pathogens or apoptotic insults. After exogenous administration, MSCs relocate to the site of injury mainly inflamed or disrupted blood vessels. In these sites, MSCs generate soluble mediators promoting tissue regeneration through angiogenesis, remodeling, immune cell modification, and cellular recruitment.[4] One debatable issue in MSC-based treatment is the efficacy of the therapy. This issue is multiparametric and includes any hypothesized clinical application and biological effects such as regeneration, reconstruction, anti-inflammatory or other effects, the efficacy of MSCs to differentiate in the site, and finally, the cell-to-cell impact and the efficacy of soluble products produced by MSCs. Another debatable issue in MSC-based treatment is the potency of the treatment meaning the ability or capacity of the MSCs to achieve a particular result to a clinically meaningful degree. The origin of the MSCs (autologous or allogeneic) appears to play a significant role. Autologous transplantations prevent problems of cross-matching, or contamination/malignancy and therefore offer an ulterior degree of safety. However, the availability of autologous MSCs is very often limited sometimes due to the disease itself. Allogeneic transplantations avoid the aforementioned issue but raise concerns related to cross-reactivity and longitudinal effectiveness. Every MSCs-donor has a distinct genetic and physiologic pattern unique for this specific donor and the soluble mediators generated by the donor-MSCs may differ significantly between different donors (even among same gender and age-matched donors)[5] with immediate effect on the potency of the treatment. Xenogeneic transplantation for research purposes is widely used but forms an even more uncontrolled environment in the context of results extraction. Defining and measuring the efficacy and potency of the treatment and the evaluation of the overall clinical impact of MSCs treatment is a challenge for all researchers in the field.

As the international literature provides an increasing bulk of evidence that MSCs such as hWJ-MSCs may alleviate or even cure several chronic diseases, it is mandatory to further investigate this novel potential therapeutic option as an adjunct tool in the armamentarium of the clinical physician.

COMPETING INTERESTS

All authors declare no competing interests.

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