Published in final edited form as:
Eur Urol. 2013 March ; 63(3): . doi:10.1016/j.eururo.2012.10.049.

Adipose-Derived Stem Cells for the Treatment of Peyronie's Disease?

Ching-Shwun Lin and **Tom F. Lue**
Knuppe Molecular Urology Laboratory, Department of Urology, School of Medicine, University of California, San Francisco, CA 94143-0738, USA

Keywords

Adipose-derived stem cells; Peyronie's disease; Xenogeneic transplantation

First identified in bone marrow, mesenchymal stem cells (MSCs) are now known to reside in most adult tissues. In particular, the adipose tissue-derived MSC (ADSC) is a highly promising cell type for clinical applications due to its ease of isolation from an abundant tissue source [1]. In urology, ADSC studies have gradually outnumbered other MSC studies in recent years, and this trend is especially evident in the erectile dysfunction (ED) field. Specifically, in our recent review article we identified a total of 15 preclinical ED-related stem cells studies [2]. Today, in less than a year, the number has grown to 24; and all but one of the new studies used ADSC as the therapeutic cell type. In addition, although not specifically targeting ED per se, a recent study used ADSC to seed small intestinal submucosa (SIS) and found that such a grafting material was superior to unseeded SIS for penile tunica albuginea (TA) reconstruction [3].

While past stem cell-for-ED studies have focused mostly on cavernous nerve injury- or diabetes-associated ED [2], a recent study has uniquely targeted Peyronie's disease (PD) and PD-associated ED [4]. In this study, simulation of PD in the rat was done by injection of TGF-β in the TA, as demonstrated by us previously [5]. One day later, human ADSC was injected in the same location; and 5 weeks later, erectile function, penile histology, and protein expression were assessed. Such an experimental design requires explanation for two of the approaches - one is the use of a xenogeneic (human) ADSC, and the other is the short (one day) period between TGF-β and ADSC injections.

In regard to the use of human ADSC, it should be noted that this is the first time in ED research that xenogeneic cells were transplanted into immunocompetent animals without the use of immunosuppressants. Although less laborious than autologous transplantation, this approach is definitely unconventional and thus demands an explanation. In Discussion the authors said: "The current use of xenogenic stem cells can be regarded as a limitation but poses a translational advantage and was used with excellent results in rats previously". However, such a statement can be interpreted as suggesting the use of xenogeneic ADSC in clinical applications. More importantly, it does not address why MSCs can be employed in a xenogeneic fashion. Thus, for readers who are not familiar with this issue, a little more explanation with credible references would be helpful. Specifically, MSCs, including ADSCs, have been shown to be immunomodulatory and immunosuppressive; and their

Dr. Ching-Shwun Lin, Department of Urology, University of California, San Francisco, CA 94143-0738, USA, Phone: 415-476-3800, Fax: 415-476-3803, clin@urology.ucsf.edu.
Dr. Tom F. Lue, Department of Urology, University of California, San Francisco, CA 94143-0738, USA, Phone: 415-476-1611, Fax: 415-476-8849, tlue@urology.ucsf.edu

xenogeneic transplantation in immunocompetent animals has been extensively reviewed in our recent article [6].

In regard to the short duration between TGF-β and ADSC injections, the authors acknowledged its lack of relevance in terms of using ADSC for the treatment for PD. Specifically, while ADSC was injected in the acute phase of TGF-β-induced tissue inflammation, PD patients are typically presented in the chronic phase. And, as mentioned above, MSCs are well known for their immunomodulatory (anti-inflammatory) capacity; therefore, in retrospect, the prevention of fibrosis in ADSC-treated rats was predictable. But, prospectively, whether ADSC can reverse (as opposed to "prevent") PD progression has become the only truly relevant issue.

To assess the effects of TGF-β and ADSC on the TA, several histological and western blot analyses were performed. In all but one of the histological images the magnification was 40x, and at such a low magnification, it is impossible to appreciate the numerous cellular and extracellular features described in the figure legends. Thus, for the sake of matching words with actions, higher-magnification (400x) histological data should be presented as supplemental materials. In regard to the western blot analysis, it is not known why collagen-III was examined but collagen-I was not. Is collagen-III upregulation characteristic of PD? As for elastin, its upregulation by TGF-β in TA-derived cells has been demonstrated previously [7] and the citation of this study would have nicely corroborated the new data. On a side note, the western blot data look unusual in that the protein bands are white while the background black. Such images are confusing in that they give the impression of RT-PCR data instead of western blot.

For the purpose of tracking the transplanted cells, EdU was used as a label, as first introduced by us in 2009 [8]. Compared to its predecessor BrdU, this new label can be detected with ease, speed, and specificity. In a soon-to-be published study we further demonstrated that EdU did not affect cell proliferation, differentiation, cytokine secretion, or migratory response [9]. Thus, the present study's demonstration of the presence of EdU-labeled cells 5 weeks after their transplantation is an independent support for EdU as a superb cell-tracking label. However, since the transplanted cells are of human origin, their tracking can also be done without any exogenously added label. That is, they could have been tracked by the detection of a human-specific protein such as laminin.

As for why ADSC could prevent TA fibrosis, the authors cited several studies to support their view of a paracrine mechanism through which MSCs might exert their therapeutic effects. However, they also said that three studies have demonstrated the kidney to be an exception to this rule. The accuracy of this statement cannot be assessed because no references were cited for those three studies. In any event, we would like to inform the reader that in our recent review article we have extensively discussed the issue of paracrine-versus-differentiation, and in these discussions we presented evidence that many claims of cell differentiation/engraftment in various tissues, including the kidney, were based on leaky cell-tracking labels, inadequate histology, and/or misinterpretation of data [10].

All in all, this study is interesting and can potentially expand the therapeutic range of ADSC, but several issues as outlined above need to be further addressed. Among them the question of whether ADSC can be used to treat PD is most important.

References

1. Lin, CS.; Lue, TF. Adipose-Derived Stem Cells: Characterization and Application in Urology. In: Illouz, YG.; Sterodimas, A., editors. Adipose Stem Cells and Regenerative Medicine. New York, NY: Springer; 2011. p. 193-207.

2. Lin CS, Xin ZC, Wang Z, et al. Stem cell therapy for erectile dysfunction: a critical review. Stem cells and development. 2012; 21:343–51. [PubMed: 21793654]

3. Ma L, Yang Y, Sikka SC, et al. Adipose tissue-derived stem cell-seeded small intestinal submucosa for tunica albuginea grafting and reconstruction. Proceedings of the National Academy of Sciences of the United States of America. 2012; 109:2090–5. [PubMed: 22308363]

4. Castiglione F, Hedlund P, Van der Aa F, et al. Intratunical Injection of Human Adipose Tissue-derived Stem Cells Prevents Fibrosis and Is Associated with Improved Erectile Function in a Rat Model of Peyronie's Disease. European urology. 2012

5. El-Sakka AI, Hassan MU, Nunes L, Bhatnagar RS, Yen TS, Lue TF. Histological and ultrastructural alterations in an animal model of Peyronie's disease. British journal of urology. 1998; 81:445–52. [PubMed: 9523668]

6. Lin CS, Lin G, Lue TF. Allogeneic and xenogeneic transplantation of adipose-derived stem cells in immunocompetent recipients without immunosuppressants. Stem cells and development. 2012; 21:2770–8. [PubMed: 22621212]

7. Lin G, Shindel AW, Banie L, et al. Pentoxifylline attenuates transforming growth factor-beta1-stimulated elastogenesis in human tunica albuginea-derived fibroblasts part 2: Interference in a TGF-beta1/Smad-dependent mechanism and downregulation of AAT1. The journal of sexual medicine. 2010; 7:1787–97. [PubMed: 20384945]

8. Lin G, Huang YC, Shindel AW, et al. Labeling and tracking of mesenchymal stromal cells with EdU. Cytotherapy. 2009; 11:864–73. [PubMed: 19903099]

9. Ning H, Albersen M, Lin G, Lue TF, Lin CS. Effects of EdU Labeling on Mesenchymal Stem Cells. Cytotherapy. 2012

10. Lin, CS.; Lue, TF. Adipose-Derived Stem Cells: Therapy through Paracrine Actions. In: Hayat, MA., editor. Stem Cells and Cancer Stem Cells. New York, NY: Springer; 2012. p. 203-16.