Autologous Mesenchymal Stem Cell Transplantation in Male Stress Urinary Incontinence

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Radical prostatectomy is the most traditional treatment for prostate cancer, which affects one out of every seven men. One of the most common side effects of a radical prostatectomy is stress urinary incontinence. [1] A 2010 study states that at 6 weeks after surgery, 59% (405) of men were incontinent, defined as any pad use. At 58 weeks after surgery, 22% (165) of men were incontinent. At 58 weeks incontinence was more prevalent in men who were obese and physically inactive (59% incontinent). Physical activity may offset some of the negative consequences of being obese because the prevalence of incontinence at 58 weeks was similar in the obese and active (25%), and nonobese and inactive (24%) (incontinent) men. The best outcomes were in men who were nonobese and physically active (16% incontinent). Men who were not obese and were active were 26% less likely to be incontinent than men who were obese and inactive (RR 0.74, 95% CI 0.52–1.06). [2]

Furthermore, almost 10% of patients experience urinary incontinence permanently. Conservative treatment for stress urinary incontinence in men consists of pelvic floor exercises. In cases when conservative treatment is unsuccessful, “urethral bulking agents, male slings, and the artificial urinary sphincter” can be used. Stem cells have proven to have regenerative effects and have been looked into as a treatment for urinary incontinence in women, by using stem cells to repopulate missing smooth muscle in the pelvic floor muscles. [3] Therefore, it is necessary to look into stem cells as a possible treatment for male urinary incontinence.

An animal trial is a necessary step in accessing how safe and effective a possible drug can be. Generally, it is difficult to find a mouse model that displays incontinence. Previous animal models used to test stem cell treatments for urinary incontinence involved artificially creating incontinent mice. [3] In order to determine if a mouse is urinary incontinent, one can observe the urination pattern of a mouse model in a cage. Generally, mice urinate in one or two discriminate locations, which can be observed by placing filter paper on the bottom of the cage. When a mouse is urinary incontinent, there would be spots on the filter paper indiscriminately. [4] There is an animal model that is currently being used in a bladder cancer study associated with New York Medical College and other institutions that display the indiscernible urination pattern, and have been determined to be an excellent model of urinary incontinence. The goal of the summer was to determine how to consistently produce smooth muscle cells from mouse bone marrow.

Following review of literature, Transforming Growth Factor Beta (TGF-ß) was decided to be the cytokine of choice. It has been proven that TGF-ß can cause smooth muscle cell differentiation through the SMAD2/SMAD3 pathway and its role in increasing the expression of myocardin, another factor in smooth muscle differentiation. Both TGF-ß1 and TGF-ß3 were investigated throughout the study. Finally, the project was attempted to find the ideal conditions for smooth muscle cell differentiation using the TGF-ß pathway.

**HYPOTHESIS**

Mesenchymal stem cells may be useful in the treatment of post prostatectomy stress urinary incontinence by populating sphincteric scar with viable smooth muscle cells.

**METHODS**

**Bone Marrow Derivation.**

Animal protocols were approved by the Institutional Animal Care and Use Committee at New York Medical College. Standard protocol was followed to remove the bone marrow from the mice. [5] Following collection of bone marrows, a Ficoll-Paque gradient was used to separate the cells in bone marrows by density. The mesenchymal stem cells were collected from the gradient and resuspended in Iscove Modified Dulbecco’s Media (IMDM) with 20% FBS at a concentration of 10^6 cell per ml of serum in petri dishes. The cells were cultured for three weeks and fed every three days.

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**RESULTS**

Immunostaining was used to test the presence of smooth muscle differentiation. By observing the characteristics expressed, one could determine if the mesenchymal stem cells had been differentiated into smooth muscle cells. An example of immunostains seen in a differentiated colony of smooth muscle cells and another smooth muscle marker, calponin, are shown in figure 1. Figure 2 shows the presence of calponin, another smooth muscle marker, in a different colony of cells treated by TGF-ß3. The images above were captured by a confocal microscope. The blue Dapi stains the nuclei while the green FITC stain are antibodies for calponin. The Image above shows presence of calponin in the treated cells.

**RESULTS CONTINUED**

The study found that while TGF-ß1 is not an optimal cytokine to consistently produce smooth muscle cells, TGF-ß3 is. Additionally, it was determined that though the previous study that used TGF-ß3 treated the cells for only 24-hours, it is more optimal to treat the cells for 48-hours or 72-hours. The next step of the project is to inoculate the smooth muscles into the urinary incontinent mouse model and see the results.

**CONCLUSIONS**

BIBLIOGRAPHY

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