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A COMPARISON OF CELLULAR AND ACELLULAR (CHEMOKINE) THERAPY IN A PRIMATE MODEL OF URINARY SPHINCTER DEFICIENCY

Hypothesis / aims of study
Urinary sphincter deficiencies in women can lead to incontinence and is associated with significant impairment of quality of life, social isolation and depressive symptoms. The underlying pathology is associated with damage to the innervation of the striated (rhabdosphincter) and/or age-related loss of sphincter muscle cells. Treatments for sphincter deficiencies are not adequate and alternatives are needed. This has led consideration of cell therapy to support regeneration of the damaged muscle as well as re-establish tissue supporting innervation and vascularization. Preclinical and clinical studies support short-term efficacy of this therapy. However, autologous cell therapy requires biopsy and lengthy cell expansion protocols. Additionally, it is unclear if cells remain at the site of injection in sufficient numbers to constitute the bulk of the regenerated tissue. A recent concept is that chemokines produced by cells are responsible, in large part, for tissue regeneration through attraction of native cells to the damaged tissues. As such, the goal of this study was to compare the effects of cell therapy and chemokine therapy on regeneration of urinary sphincter structure and function in a primate model of induced sphincter deficiency.

Study design, materials and methods
Urinary sphincter deficiency was created in 45 adult female cynomolgus monkeys by selectively cauterizing and then transecting its pudendal innervation. Five million autologous green fluorescence protein (GFP)-labeled skeletal muscle precursor cells were injected into the sphincter complex within 6 weeks post injury in ½ of the monkeys. Additionally, 6 monkeys received sphincteric injections of the chemokine, stromal derived factor-1α (CXCL-12) (100µg), or a collagen solution, instead of cells. Maximal urethral pressure (MUP) was measured in all animals at baseline and at 3 and 6 months post sphincteric injections. Urinary sphincters were examined histologically at 3 or 6 months post injection for muscle and collagen content, presence and distribution of injected (GFP^+) vs. native cells, presence of vascular structures, somatic and adrenergic innvervation, and cell immunohistochemical phenotype.

Results
Pudendal nerve transection produced sustained reductions in MUP, sphincteric muscle content, vascularity and innervations over 6 months in the non-cell/no CXCL-12 treated monkeys. Both cell and CXCL-12 injections restored these measures to baseline, or those of uninjured control monkeys. All cells within the regenerating sphincter complex of treated animals expressed appropriate muscle-specific proteins (skeletal muscle actin, smoothelin) in the skeletal and smooth muscle layer of the sphincter complex and urothelial cell markers (uroplakins, cytokeratins). Labeled (GFP^+) cells could be found incorporating into the skeletal and smooth muscle layers, the vasculature and the urothelium, but only in small numbers (5-10% of the total). There was marked expression of CXCL-12 by injected and native cells within the sphincter complex.

Interpretation of results
Both injected cells and chemokine produced improvement in structure and function in this model of sphincter deficiency. In fact, CXCL12 may have produced somewhat better results, but the numbers of animals were small. Of note is that the monkeys receiving CXCL12 had longer-standing sphincter deficiency (5 months) than the cell-treated monkeys (average 2 months), thus raising the possibility that CXCL12 may be beneficial in patients with long-standing sphincter deficiency.

Concluding message
While producing moderate success, the cell collection and expansion process needed for cell therapy of UI is laborious, expensive and is confounded by hesitant FDA approval. We now propose a safer, cheaper therapy that utilizes a new aspect of regenerative medicine called regenerative pharmacology to meet this unmet need.

Disclosures
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