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DIFFERENTIAL GENE EXPRESSION IN POSTMENOPAUSAL WOMEN WITH STRESS URINARY INCONTINENCE

Hypothesis / aims of study
To compare differential gene expression in postmenopausal women with and without stress urinary incontinence (SUI).

Study design, materials and methods
This pilot study was designed to evaluate the feasibility of gene expression analysis for stress urinary incontinence in postmenopausal women and to provide preliminary data regarding differential gene expression in these subjects. The Institutional Review Board approved this study. Informed consent was obtained from all subjects at the time of enrolment. All women were postmenopausal and none of the subjects had pelvic organ prolapse beyond stage one. Three women had SUI and were undergoing continence surgery; the two controls were continent and undergoing gynecologic surgery unrelated to continence or prolapse. Women in both groups were matched for age and race. Full thickness biopsies of the vaginal mucosa underlying the urethrovesical junction were obtained using a 7 mm punch biopsy tool. Each biopsy specimen was homogenized in Trizol reagent for extraction of total RNA. Samples were processed for high density oligonucleotide array analysis. Microarray analysis was performed on each biopsy specimen using Affymetrix high-density oligonucleotide arrays. A variety of probe level normalization and statistical analysis tools were used to generate profiles of differentially expressed genes. Differences in gene expression of more than two-fold were considered for further evaluation. Genes were selected by statistical significance, fold-change, biological relevance and by family group.

Results
All vaginal biopsy samples were of adequate size and quality for RNA extraction and microarray analysis. A total of 54,675 genes were interrogated. In women with SUI, a total of 1788 genes were over-expressed compared with controls. Of these, 1,465 genes were over-expressed by more than 2-fold, 248 by more than 4-fold, and 75 by more than 8-fold. Under-expressed compared to controls were a total of 1,676 genes. Of these, 1,400 genes were under-expressed by 2-fold, 233 by 4-fold, and 43 by 8-fold. S100 calcium binding protein A7 (S100A7), a gene involved in regulation of cell cycle progression and differentiation, was more than 200 times over-expressed in women with SUI. Small proline-rich protein 2C (SPRR2C), involved in keratinocyte differentiation, was more than 160 times over-expressed in women with SUI compared to controls. Also over-expressed more than 50 times compared to controls was kallikrein 7 (KLK7) a protease involved in epidermal differentiation. FBJ murine osteosarcoma viral oncogene homolog (FOSB), a gene involved in cell differentiation and proliferation, was 26 times underexpressed in women with SUI. Protocadherin 8 (PCDH8), involved in cell adhesion, was 33 times underexpressed in women with SUI compared to controls. Within the collagen family of proteins, Collagens XXIVα1 and XXVα1 were under-expressed more than 3-fold compared to controls. Procollagen C-endopeptidase enhancer, a glycoprotein involved in the assembly of fibrillar collagens in the extracellular matrix, was more than 9-fold over-expressed in women with SUI. In these women, collagens XXVIIα1, Vα2, IVα2, and IVα1 were each more than 2-fold over-expressed. Collagen family proteins involved in post-translational modification of procollagen, cell adhesion, and fibroblast apoptosis were also over-expressed in women with SUI compared to controls.

Interpretation of results
There are differences in gene expression between postmenopausal women with stress urinary incontinence and those without. Each woman with SUI exhibited a similar pattern of up and down regulation when compared to continent controls. Differentially expressed genes included those involved with cell proliferation and differentiation, cell adhesion, and extracellular matrix organization, which all may impact on structural support. However, interpretation of the findings of this study is limited because of the small number of subjects. Therefore, genes selected from this analysis will be validated by quantitative PCR and pathways will be probed for molecular mechanism validation.

Concluding message

Our preliminary findings suggest that differences exist in the expression of genes in women with and without SUI. Differentially expressed genes within the collagen family of proteins may lead to structural changes in the support tissues contributing to stress urinary incontinence.

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