Sphingosine-1-phosphate Dysregulation And The Development Of Pelvic Organ Prolapse (Poster)

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INTRODUCTION & OBJECTIVES

- Pelvic Organ Prolapse (POP) is a disorder that occurs when the musculature of the pelvic floor weakens, resulting in pathologic descent of pelvic organs into the vaginal canal.
- While risk factors for POP have been suggested such as genetic predisposition, childbirth, obesity, and advancing age, the etiology of this condition remains largely unknown.
- Females have an 11% lifetime risk of POP which can result in urinary, bowel, and sexual dysfunction that can significantly impair a woman’s quality of life.¹
- Sphingosine-1-Phosphate (SIP) is a bioactive lysosphingolipid with countless metabolic functions including regulation of cell proliferation and smooth muscle (SM) contractility.² SIP is generated by the phosphorylation of sphingosine by sphingosine kinase, which exists as two major isoforms (SPHK1 & SPHK2).
- We hypothesized that SPHK isoform expression could be altered in vaginal SM, thereby leading to decreased vaginal wall stability and subsequent POP.

BACKGROUND

Pelvic Organ Prolapse (POP) is a disorder that occurs when the musculature of the pelvic floor weakens, resulting in pathologic descent of pelvic organs into the vaginal canal. While risk factors for POP have been suggested such as genetic predisposition, childbirth, obesity, and advancing age, the etiology of this condition remains largely unknown. Females have an 11% lifetime risk of POP which can result in urinary, bowel, and sexual dysfunction that can significantly impair a woman’s quality of life.¹ Sphingosine-1-Phosphate (SIP) is a bioactive lysosphingolipid with countless metabolic functions including regulation of cell proliferation and smooth muscle (SM) contractility.² SIP is generated by the phosphorylation of sphingosine by sphingosine kinase, which exists as two major isoforms (SPHK1 & SPHK2). We hypothesized that SPHK isoform expression could be altered in vaginal SM, thereby leading to decreased vaginal wall stability and subsequent POP.

METHODS

- Anterior vaginal wall smooth muscle and epithelial tissue samples were obtained from women undergoing surgery at Cooper University Hospital.
- Control Samples: obtained from women undergoing routine hysterectomy with no history of POP
- Experimental Samples: obtained from women with POP undergoing reconstructive surgical repair
- Tissue samples were extracted into SDS-PAGE sample buffer. Quantitative Western Blot analyses using Bio-Rad’s No-Stain Gel line/Trans-Blot Turbo Blotting System/Chemidoc Imager/Image Lab 6.0 software and fluorescently tagged antibodies were used to determine relative expressions of SPHK1, SPHK2, & SPP1.
- Total Protein Normalization (Fig. A): Relative expression of target protein to total lane protein visible on ultraviolet light-activated bio-stain was determined which minimized the effects of unequal loading between lanes.

RESULTS

- SPHK1 expression 46% lower in POP compared to controls normalized to total protein
- SPHK1 expression 40% lower in POP compared to controls normalized to total protein

DISCUSSION & CONCLUSIONS

- Our novel data suggests that SPHK1 is the predominant sphingosine kinase in human anterior vaginal SM and epithelial tissue samples and that its levels are decreased dramatically in women with POP compared to controls.
- Levels of SPHK1 were also found to be lower in vaginal wall smooth muscle (but only slightly). The larger decrease in SPHK1 vs SIP1 expression would suggest a shift toward a higher sphingosine-to-SIP1 ratio and thus a shift toward apoptosis and cell cycle arrest and overall decreased vaginal wall stability.
- These findings suggest a POP preventative treatment strategy of stabilizing SPHK1 levels in the vagina.
- Our study utilized human samples making our findings translationally relevant.
- A limitation of our data is that only 5 control and 5 POP human samples were utilized. More samples will be analyzed in the future.

REFERENCES