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Global Transcriptome Analysis of Response to Uropathogenic E. coli Infection in a Murine Menopause Model

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Urinary tract infections (UTIs), which are primarily caused by uropathogenic Escherichia coli (UPEC), annually affect over 150 million patients worldwide. Despite efforts with antibiotic therapies, women, particularly post-menopausal women, frequently suffer from recurrent and persistent UTIs, suggesting that estrogen status is a risk factor. Previously, our group showed that estrogen status alters the normal course of infection. The objective of this project was to determine how estrogen status governs susceptibility to UTIs and which molecular signals were specifically responsible for mediating the estrogenic control. We used a mouse model of surgical menopause to mimic the estrogen levels found in post-menopausal women (OVX); control animals pre-menopausal (SHAM). To identify the genes responsible for the differences seen in SHAM mice and OVX mice during a UTI, we performed global gene expression analysis using Illumina DNA microarray analysis. Next, using Ingenuity Pathway analyses, I identified ten pathways and associated genes which were most affected by ovariectomy in response to UPEC infection. These included genes modulating immune response, cytoskeletal remodeling, and stem-cell regulatory pathways (WNT) pathways. Finally, I used quantitative real time PCR validation analyses to demonstrate that IL-17, CD44, and Tcf19 expression displayed significant differential regulation by estrogen. Thus, my findings reveal that a menopausal state, i.e., estrogenic deficiency particularly affects genes involved in both inflammation and epithelial stem-cell regulation in the bladder in response to UPEC infection. By identifying the genes responsible for the differences in non-menopausal and menopausal females, we hope to elucidate the mechanisms underlying these differences and establish a link between basic science and clinical practice to better address the clinical burden of UTIs in post-menopausal women.