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May 8th, 12:30 PM - 1:30 PM


## Cxcl-Type Chemokines-Induced Fibrosis In The Lower Urinary Tract

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Gharaee-Kermani M, Macoska JA. (2013). Cxcl-Type Chemokines-Induced Fibrosis In The Lower Urinary Tract. UMass Center for Clinical and Translational Science Research Retreat. Retrieved from [https://escholarship.umassmed.edu/cts\\_retreat/2013/posters/53](https://escholarship.umassmed.edu/cts_retreat/2013/posters/53)

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## **CXCL-TYPE CHEMOKINES-INDUCED FIBROSIS IN THE LOWER URINARY TRACT**

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**Introduction:** Recent studies from our group suggest that extracellular matrix (ECM) deposition and fibrosis characterize the peri-urethral prostate tissues of some men suffering from Lower Urinary Tract Symptoms (LUTS). Fibrosis can generally be regarded as an errant wound-healing process in response to chronic inflammation, and studies have shown that the aging prostate tissue microenvironment is rich with inflammatory cells and proteins. However, it is unclear whether these same inflammatory proteins, particularly CXC-type chemokines, can mediate myofibroblast phenoconversion and the ECM deposition necessary for the development of prostatic tissue fibrosis.

**Methods:** Peri-urethral prostate tissues were disaggregated and subjected to FACS for expression of CD45 and collagen I. Primary stromal fibroblasts were cultured from explanted human peri-urethral prostatic tissues. N1 immortalized or primary prostate stromal fibroblasts were treated in serum-free defined media with TGF- $\beta$ , CXCL5, CXCL8, or CXCL12 and evaluated using immunofluorescence or qRT-PCR for  $\alpha$ SMA, collagen I, collagen III, vimentin, calponin, and tenascin protein and transcript expression, and by gel contraction assays for functional myofibroblast phenoconversion. The specificity of these responses to treatment with CXCL12 was assessed using a small molecule inhibitor, AMD3100, of the CXCL12 receptor, CXCR4.

**Results:** The results of these studies showed that peri-urethral prostate tissues comprised both myofibroblastic and fibroblastic cell types, but that CD45+/collagen I+ fibrocytic cells were identified exclusively in peri-urethral tissues from men suffering from LUTS. Both N1 immortalized and primary prostate stromal fibroblasts exhibited complete and functional myofibroblast phenoconversion and were induced to express collagen I, collagen III and  $\alpha$ SMA gene transcripts and proteins in response to treatment with CXC-type chemokines, even in the absence of exogenous TGF- $\beta$ 1.

**Conclusions:** These findings suggest that CXC-type chemokines, particularly CXCL12, can efficiently and completely mediate myofibroblast phenoconversion and may thereby promote fibrotic changes in prostate tissue architecture associated with the development and progression of male lower urinary tract dysfunction.

Supported by MICHR grant U034697 (MGK) and NIH/NIDDK grant 1P20DK090870-03 (JAM)