Prostate-specific deletion of Cdh1 induces murine prostatic inflammation and bladder overactivity

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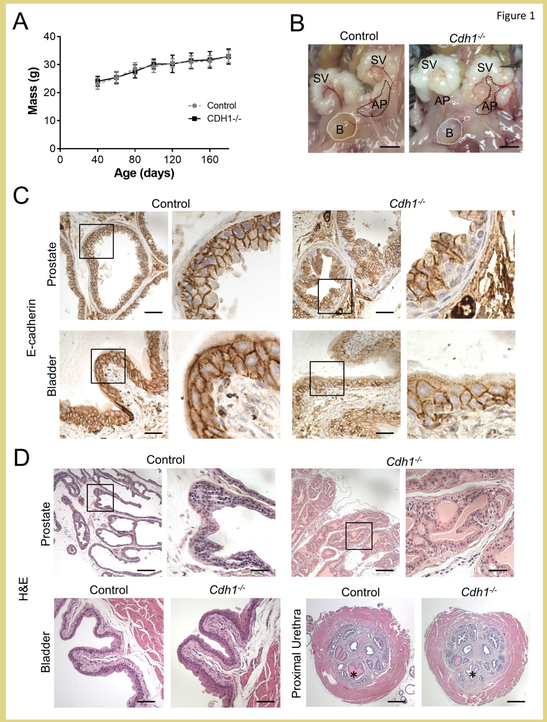
Abstract

Benign Prostatic Hyperplasia (BPH) is an age-related debilitating prostatic disease that is frequently associated with prostatic inflammation and bothersome lower urinary tract symptoms (LUTS). Animal models have shown that formalin- and bacterial-induced prostatic inflammation can induce bladder dysfunction; however, the underlying mechanisms contributing to prostatic inflammation in BPH and bladder dysfunction are not clear. We previously reported that E-cadherin expression in BPH is down-regulated in hyperplastic nodules compared to expression in adjacent normal tissues. Here, we explored the potential consequences of prostatic E-cadherin down-regulation on the prostate and bladder in vivo using an inducible murine model of prostate luminal epithelial-specific deletion of Cdh1. The PSA-CreERT2 transgenic mouse strain expressing tamoxifen-inducible CreERT2 recombinase driven by a 6-kb human PSA promoter/enhancer was crossed with the B6.129-Cdh1tm2Kem/J mouse to generate bigenic PSA-CreERT2/Cdh1-/- mice. Deletion of E-cadherin was induced by transient administration of tamoxifen when mice reached sexual maturity (7 weeks of age). At 21-23 weeks of age, the prostate, bladder, and prostatic urethra were examined histologically, and bladder function was assessed using Void Spot Assays and cystometry. Mice with Cdh1 deletion had increased prostatic inflammation, prostatic epithelial hyperplasia and stromal changes at 21-23 weeks of age, as well as changes in bladder voiding function compared to age-matched controls. Thus, loss of E-cadherin in the murine prostate could result in prostatic defects that are characteristic of BPH and lower urinary tract symptoms, suggesting that E-cadherin down-regulation could be a driving force in human BPH development and progression.

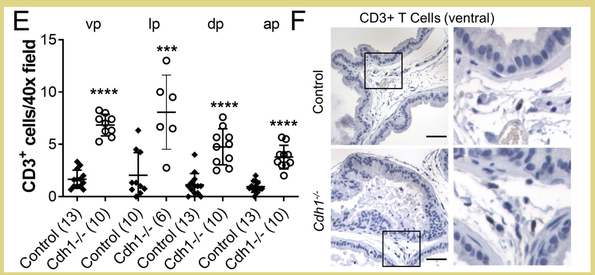
Funding

We thank Dr. Pierre Chambon and Dr. Daniel Metzger (IGBMC, Illkirch, France) for generously providing the PSA-CreERT2 mouse for this study. We are grateful to Anthony Green, Megan Lambert, Robin Frederick, Elaine Isherwood, Paul Knizner, Jianhua Zhou and Aiyuan Zhang for technical support. This work was funded in part by NIH grants U54 from NIDDK, DK112079 (ZW), R56 DK107492 (ZW), and 1R50 CA211242 (LEP), and by an American Urology Association Award (WC). This project used the Tissue Resources and Morphology Core (TRMC) of the O'Brien Urology Research Center at University of Pittsburgh (DK112079). This project used the UPCI Animal Facility and the Pitt Biospecimen Core and was supported in part by award P30CA047904.

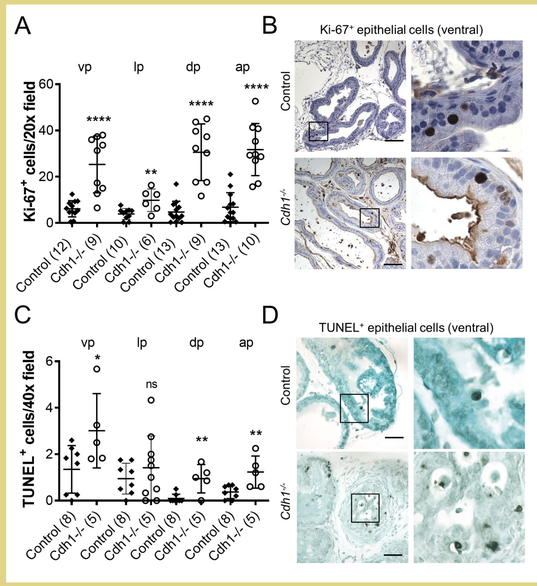
Prostate epithelial specific E-cadherin loss on the lower urogenital tract of male mice

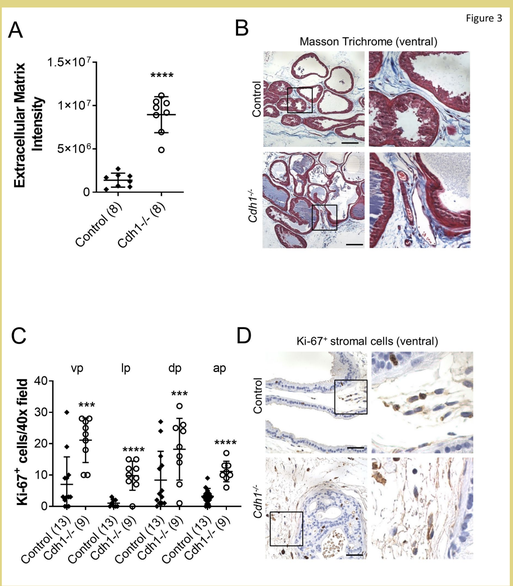


Increased prostatic inflammation



Prostate: Increased epithelial proliferation and apoptosis (left panel) Increased fibrosis and stromal proliferation (right panel)





Bladder: Increased voiding (left panel) and Increased non-voiding contractions (right panel)