AB012. E-cadherin is down-regulated in benign prostate hyperplasia and required for tight junction formation and permeability barrier in prostatic epithelial cell monolayer

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Background: Prostate specific antigen (PSA), which is expressed by luminal epithelial cells in prostate was recently shown in the stromal compartment of benign prostatic hyperplasia (BPH). Since the stromal compartment does not express PSA, epithelial barrier integrity in BPH nodules might be compromised through loss of cell junctions, resulting in the leakage of PSA and other secreted proteins into the stromal compartment and subsequently promoting BPH pathogenesis. E-cadherin, an important cell junction regulator, is found to be down-regulated in epithelial cells in clinical BPH specimens. Whether E-cadherin downregulation affects epithelial barrier permeability is unknown. This research is aimed at examining epithelial barrier permeability change in BPH and exploring the potential role of E-cadherin in prostatic luminal epithelial permeability.

Methods: Explants derived from BPH patients were used to study epithelial barrier permeability in BPH nodules and its normal adjacent tissues by FITC-dextran assay. These specimens were also used to study tight junctions in BPH nodules and normal prostate tissues using transmission electron microscopy (TEM), and used to study the expression of junctional proteins ZO-1, ZO-2, ZO-3 and E-cadherin using immunofluorescence staining. The expression of E-cadherin in these specimens was also determined by immunohistochemistry staining. Normal prostatic luminal epithelial cell lines BHPrE-1 and BPH-1 were utilized to perform *in vitro* studies. Two independent siRNAs were used to knockdown E-cadherin expression. Permeability and tight junctions of cell monolayers in trans-well inserts with/without E-cadherin knockdown were evaluated by trans-epithelium electrical resistant (TER) assay and FITC-dextran trans-well assay, and TEM respectively. Expression of E-cadherin following siRNAs treatment was determined by reverse transcription-polymerase chain reaction (RT-PCR) and western-blot (WB).

Results: FITC-dextran assay detected an increased epithelial barrier permeability in BPH tissues but not in the adjacent normal prostate in explants derived from BPH patients. Tight junctions as well as junctional proteins were decreased in BPH tissues as compared to the normal prostate, suggesting the compromise of luminal epithelial barriers in BPH. E-cadherin was down-regulated and displayed a discontinuous pattern in BPH. E-cadherin expression was negatively correlated with prostatic epithelial monolayer permeability, and E-cadherin knockdown increased monolayer permeability and disrupted tight junction formation.

Conclusions: Epithelial barrier permeability is increased in BPH and loss of E-cadherin is potentially an important underlying mechanism, suggesting blocking E-cadherin loss could be a potential approach to prevent or treat BPH.

Keywords: benign prostatic hyperplasia (BPH); epithelial barrier; permeability; tight junction; E-cadherin

doi: 10.21037/tau.2018.AB012

Cite this abstract as: Li F, Pascal LE, Parwani A, Dhir R, Nelson JB, Guo P, He D, Wang Z. E-cadherin is down-regulated in benign prostate hyperplasia and required for tight junction formation and permeability barrier in prostatic epithelial cell monolayer. Transl Androl Urol 2018;7(Suppl 5):AB012. doi: 10.21037/tau.2018.AB012

