Claudin-1 is down-regulated in the aging prostate and associated with increased infiltration of inflammatory cells in BPH

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Abstract

Introduction and Objective: Benign prostatic hyperplasia (BPH) is an age-related disease that is frequently associated with chronic prostatic inflammation. In previous studies, we detected the presence of PSA protein in the stroma of BPH modules and down-regulation of junction proteins E-cadherin and claudin-1. Transmission electron microscopy (TEM) imaging showed a decrease in tight junctions suggesting the luminal epithelial barrier in BPH tissues may be compromised. Recent in vitro studies showed that stimulation of benign prostatic epithelial cell lines with TGFβ1 induced a decrease in claudin-1 expression suggesting that inflammation might be associated with alterations in the prostate epithelial barrier. This study explored the potential associations between aging and loss of junction proteins and the presence of inflammatory cells in prostate tissue specimens from young healthy donors and aged BPH patients.

Methods: Immunostaining of serial prostate sections from BPH patients and healthy young donors was performed for claudin-1, CD4, CD8, CD20 and CD68. H-Scores and the number of inflammatory cells were calculated for the same area in donor, normal adjacent prostate (NAP) to and BPH specimens. Quantification and statistical correlation analyses were performed.

Results: Down-regulation of junction protein claudin-1 was associated with increased age, and inflammation in NAP and BPH compared to young healthy donor prostate. B-cell infiltration increased with age and BPH was associated with an increased infiltration of T-cells and macrophages compared to NAP.

Conclusions: These findings suggest that aging is associated with down-regulation of claudin-1 and claudin-1 is further decreased in BPH. Claudin-1 down-regulation was associated with increased infiltration of inflammatory cells in both NAP and BPH tissues. Claudin-1 down-regulation in the aging prostate could contribute to increased prostatic inflammation, subsequently contributing to BPH pathogenesis.

Funding

We are grateful to Elaine V. Byrnes and Paul Knizer for technical support. This work was funded in part by NIH grants U54 from NIDDK, DK112079 (QW), R56 DK107492 (ZW), and 1R01 CA214242 (LEP), American Urology Association Award (WC). This project used the UPCI Tissue and Research Pathology Services (TARPS) and the Pitt Biospecimen Core and was supported in part by award P30CA047904 with additional support from the University of Pittsburgh Cancer Institute.

Introduction

Inflammation, fibrosis and hyperplasia are hallmarks of the aging prostate. Benign prostatic hyperplasia (BPH), a complex disease characterized by increased prostatic growth, is a common condition affecting many older men. Inflammation, subsequent to aging and the development of BPH, can contribute to increased epithelial loss, cell death and cell proliferation [1]. Studies have shown that an immunohistochemical analysis of the prostate sections in young healthy donors, normal adjacent prostate (NAP) and BPH specimens, can detect the presence of inflammatory cells and macrophages. However, the correlation between aging and inflammation in the prostate and the presence of inflammatory cells in prostate tissue specimens from young healthy donors and aged BPH patients is not fully understood.

Methods

Immunostaining of serial prostate sections from BPH patients and healthy young donors was performed for claudin-1, CD4, CD8, CD20 and CD68. H-Scores and the number of inflammatory cells were calculated for the same area in donor, normal adjacent prostate (NAP) to and BPH specimens. Quantification and statistical correlation analyses were performed.

Results

Down-regulation of junction protein claudin-1 was associated with increased age, and inflammation in NAP and BPH compared to young healthy donor prostate. B-cell infiltration increased with age and BPH was associated with an increased infiltration of T-cells and macrophages compared to NAP.

Conclusions

These findings suggest that aging is associated with down-regulation of claudin-1 and claudin-1 is further decreased in BPH. Claudin-1 down-regulation was associated with increased infiltration of inflammatory cells in both NAP and BPH tissues. Claudin-1 down-regulation in the aging prostate could contribute to increased prostatic inflammation, subsequently contributing to BPH pathogenesis.

Prostatic Inflammation

Claudin-1 correlation with age and inflammation

Table 1. Demographics of human prostate tissue specimens for immunostaining study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (range)</th>
<th>Min.</th>
<th>Max.</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67 (50-71)</td>
<td>50</td>
<td>71</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight of Prostate in grams</td>
<td>39.1 (24.1-74.3)</td>
<td>24.1</td>
<td>74.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Prostate mass</td>
<td>33.5 (30.1-36.9)</td>
<td>30.1</td>
<td>36.9</td>
<td>0.0326</td>
</tr>
<tr>
<td>BPH vs. NAP</td>
<td>0.6053</td>
<td>0.4810</td>
<td>0.2830</td>
<td>0.0271</td>
</tr>
</tbody>
</table>

*Bold indicates statistically significant between groups.*

Table 2. Comparing Donor vs. NAP and BPH vs. NAP

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Donor vs. NAP</th>
<th>BPH vs. NAP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-Score</td>
<td>0.6053</td>
<td>0.4240</td>
<td>0.0182</td>
</tr>
<tr>
<td>Claudin-1 mRNA expression</td>
<td>0.6053</td>
<td>0.4240</td>
<td>0.0271</td>
</tr>
</tbody>
</table>

*Bold indicates statistically significant between groups.*

Table 3. Correlation: Claudin-1 down-regulation with Age in the combined samples from groups

<table>
<thead>
<tr>
<th>Correlation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claudin-1 H-Score Average</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Bold indicates statistically significant between groups.*