E-cadherin is inversely correlated with aging and inflammation in the prostate

Laura E. Pascal, # and Rajiv Dhir #, Goundappa K. Balasubramani, Wei Chen, Chandler N. Hudson, Pooja Srivastava, Anthony Green, Donald B. DeFranco, Naoki Yoshimura and Zhou Wang

Abstract

Introduction and Objective: E-cadherin is critical for the development and maintenance of the prostate epithelial barrier and is frequently down-regulated in prostatic disease. Previous studies have shown that E-cadherin is down-regulated in benign prostatic hyperplasia (BPH) and may contribute to increased epithelial permeability and subsequent prostatic inflammation. BPH is an age-related disease but the mechanisms contributing to BPH pathogenesis have not been fully elucidated. Decline of epithelial barrier function has been associated with aging, inflammation and age-related diseases. Thus, this study explored the potential associations between aging and loss of E-cadherin and the presence of inflammatory mediators in prostate tissue specimens.

Methods: Serial prostate sections from a cohort of donors aged 15-26 years and BPH patients aged 50-77 years were immunostained with E-cadherin, COX-2, CD4, CD8, CD20 and CD68. E-cadherin and COX-2 H-Scores and the number of inflammatory cells were calculated for the same area in donor, normal adjacent prostate to BPH (NAP) and BPH specimens. Quantification and statistical correlation analyses were performed for comparisons between groups.

Results: E-cadherin was decreased in aged NAP tissues and in BPH compared to young donor tissue. E-cadherin was inversely correlated with age and infiltration of inflammatory cells in NAP compared to young healthy donor prostate. Stromal COX-2 was positively correlated with age and inflammation. E-cadherin was further down-regulated in BPH, while COX-2 H-Scores were not significantly altered in BPH compared to NAP.

Conclusions: These findings suggest that aging is associated with down-regulation of E-cadherin and up-regulation of stromal COX-2 immunostaining in the prostate. E-cadherin immunostaining was inversely associated with age and inflammation, while stromal COX-2 immunostaining was positively associated with age and inflammation in the prostate. These findings suggest that the prostate epithelial barrier is altered and inflammation is increased with age in the prostate. These changes are further exacerbated in BPH, and may be involved in BPH pathogenesis.

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Age-related decrease in E-cadherin and increase in COX-2

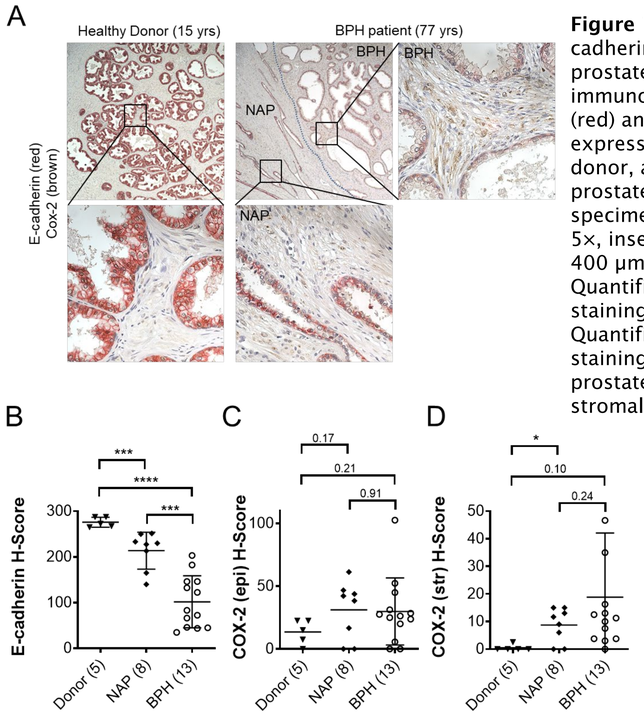

Figure 1. Expression of E-cadherin and COX-2 in the prostate. (A) Representative immunostaining of E-cadherin (red) and COX-2 (brown) expression in young healthy donor, and normal adjacent prostate (NAP) and BPH specimens. Original magnification 5×, inset 40×, scale bars indicate 400 µm in 5×, 50 µm in 40×. (B) Quantification of mean E-cadherin staining intensity H-score. (C) Quantification of mean COX-2 staining intensity H-Score in prostate epithelial (epi), and (D) stromal (str) cells. Number of patients in parentheses. Data represent mean ± S.D.; *, p<0.05; ***, p<0.001; ****, P<0.0001.

Localization of Claudin-1 and Inflammation

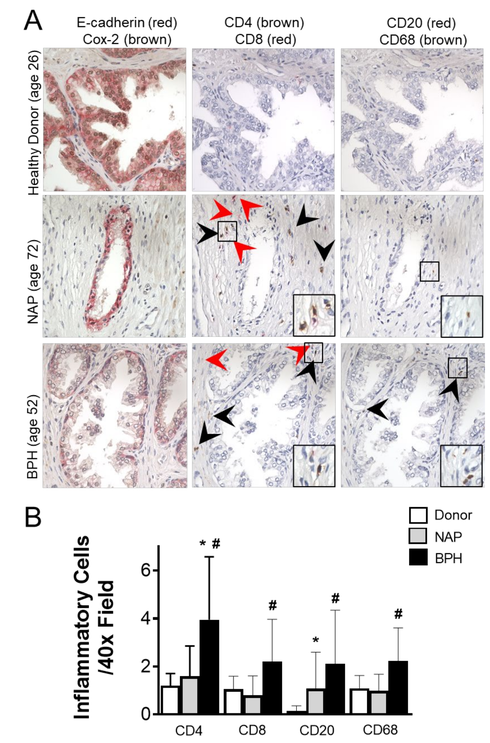

Figure 2. E-cadherin, COX-2 and infiltrating inflammatory cells in prostate. (A) Immunostaining of E-cadherin (red), COX-2 (brown), CD4 (brown), CD8 (red), CD20 (red) and CD68 (brown) in serial sections of young healthy donor, normal adjacent prostate (NAP) and BPH specimens. Age of patient in parentheses. Original magnification 40×, scale bars indicate 50 µm. (B) Quantification of the number of infiltrating inflammatory cells in donor, NAP and BPH specimens per 40× field. Data represent mean ± S.D.; *, p<0.05 compared to donor; #, p<0.05 compared to NAP.

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

	Donor	NAP	BPH
No. patients	5	8	13
Mean age (range)	20.2 (15-26)	62 (50-77)	62.5 (50-77)
Race (%):			
African-American	0 (0%)	4 (50%)	7 (54%)
Caucasian	4 (80%)	4 (50%)	6 (46%)
Unknown	1 (20%)	0 (0%)	0 (0%)

NAP: normal adjacent prostate
BPH: benign prostatic hyperplasia
No.: number

Table 2. Comparing E-cadherin and COX-2 H-Score and number of inflammatory cells per field in young healthy donor (Donor), normal adjacent prostate to BPH (NAP) and BPH tissues. Donor vs. NAP and BPH vs. NAP

Outcome	Donor (n=5) vs. NAP (n=8)			BPH (n=13) vs. NAP (n=8)		
	Median (IQR)	Median (IQR)	P value[1]	Median (IQR)	Median (IQR)	P value[1]
E-cadherin H-Score average for tissue type	272.5 (20)	228.8 (52.5)	**0.0043**	83.3 (100.3)	228.8 (52.5)	**0.001**
COX-2 staining H-score average in epithelial cells	15 (15)	40.3 (36.9)	0.2102	26.3 (11.3)	40.3 (36.9)	0.6894
COX-2 staining H-Score average in stromal cells	0 (0)	10.3 (11)	**0.0374**	11.3 (12.5)	10.3 (11)	0.5615
Prostate mass (g)	36 (9)	49.1 (47.3)	0.3142	55.4 (43.1)	49.1 (47.3)	0.481
Prostate volume (cm^3)	19.1 (2.6)	33.5 (30.2)	**0.0135**	45.4 (40.7)	33.5 (30.2)	0.6053

IQR: Inter-Quartile range (difference between third quartile – First Quartile)
[1]P value based non-parametric test using Wilcoxon Signed Rank Test due to smaller sample size
Bold indicates statistically significant between groups.
g: grams
cm3: cubic centimeters

Table 3. Pearson correlation of E-cadherin and stromal COX-2 (str) immunostaining with age and inflammatory cells in prostate

E-cadherin *vs.*	Age	COX-2 (epi)	COX-2 (str)	CD8	CD4	CD20	CD68
Pearson r							
r	-0.56	-0.28	-0.14	-0.36	-0.29	-0.45	-0.4
95% CI	-0.78 to -0.23	-0.60 to 0.13	-0.50 to 0.26	-0.66 to 0.030	-0.61 to 0.11	-0.71 to -0.073	-0.68 to -0.015
R squared	0.32	0.076	0.02	0.13	0.083	0.2	0.16
P value							
P (two-tailed)	**0.0027**	0.07	0.15	**0.022**	**0.043**	0.19	0.082
COX-2 (str) *vs.*	**Age**	**COX-2 (epi)**	**E-cadherin**	**CD8**	**CD4**	**CD20**	**CD68**
Pearson r							
r	0.39	0.39	-0.36	0.48	0.26	0.012	0.035
95% CI	0.0033 to 0.68	0.0087 to 0.68	-0.66 to 0.030	0.11 to 0.73	-0.14 to 0.59	-0.38 to 0.40	-0.36 to 0.42
R squared	0.15	0.16	0.13	0.23	0.069	0.00015	0.0012
P value							
P (two-tailed)	**0.049**	0.046	0.07	**0.014**	0.19	0.95	0.87

CI: confidence interval
Bold indicates statistically significant between groups.