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RESEARCH ARTICLE

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ZEB1 is Negatively Correlated with E-Cadherin in Prostatic Anomaly Tissue

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Background: Prostatic anomalies are common in tumor or infection condition. The enlargement of prostate gland affects the epithelial cell polarity that involves epithelial-mesenchymal transition (EMT). Transition into mesenchymal is mediated by transcription factor ZEB1 and E-cadherin protein. Upregulation of ZEB1 and loss of E-Cadherin expression were associated to proliferation and metastasis of malignancy cells. This study aims to describe the correlation of ZEB1 and E-cadherin expression in prostatic anomaly.
Materials and method: Samples were Formalin Fixed Paraffin Embedded (FFPE) block consist of 8 block Benign Prostatic Hyperplasia (BPH), 6 blocks High Grade Prostatic Intraepithelial Neoplasia (HGPIN) and 6 blocks Prostate Carcinoma (PCA). The blocks then sliced into 5 sections to be prepared for RNA extraction procedures. ZEB1 and E-Cadherin expression was analyzed by semi-quantitative procedures using PCR and electrophoresis. Correlation between ZEB1 and E-Cadherin espression was analyzed using Spearman's rank correlation.
Results: Relative expression of ZEB1 and E-cadherin mRNA in each group of prostatic anomaly were not significantly different (p>0.05). ZEB1 and E-Cadherin mRNA expression showed a significant and moderate level of negative correlation (p<0.05; $0.40 < r < 0.59$). Increasing of ZEB1 mRNA expression will be followed by decreasing of E-Cadherin mRNA expression.
Conclusion: ZEB1 negatively correlates with E-cadherin due to EMT process in prostatic anomaly. High expression of ZEB1 induced down-regulation of E-cadherin and vise versa. Various studies can be developed, especially the development of targeted therapy against ZEB1 to suppress the EMT process by increasing the expression of E-cadherin.

Keywords: *epithelial-mesenchymal transition (EMT), ZEB1, E-Cadherin, BPH, HGPIN, PCA*

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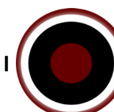

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Introduction

The prostate gland is part of male reproductive system that produce semen fluid and carry sperm from testicles when penis has ejaculating.[1] The size of prostate width, height and length tend to increase with age.[2] Several common prostatic anomaly are Benign Prostatic Hyperplasia (BPH), Prostatic Intraepithelial Neoplasia (PIN) and Prostate Adenocarcinoma (PCA). One of the most common urologic diseases is BPH, which is often found in elderly people.[3] The other prostatic gland anomaly is PIN, categorized as low grade PIN (PIN1), and high grade PIN (PIN1 or PIN2).[3,4] The anomaly that leads to PCA is High Grade Prostatic Intraepithelial Neoplasia (HGPIN). The incidence of HGPIN increases with the age of the patient. Patients with HGPIN have 15 times more risk for adenocarcinoma prostate development compared to those without HGPIN.[4] Meanwhile, it is difficult to differentiate HGPIN and PCA. Some recent studies still encounter difficulties to distinguish HGPIN from BPH because of the similarity of their morphology.[5]

PCA is the second highest occurring cancer and leading cause of death among men in America and Europe.[6] In Asia, the prevalence of prostate adenocarcinoma is 7.2 of 100,000 men each year. In Indonesia, the incidence of PCA for the last 8 years was 1,102 patients, with mean age of 67 years old and 50% found in advanced stages.[7] While localized prostate cancer is often slow-growing and clinically stable, meta-static spread lowers the possibility of survival and therapy is rarely curative. The mortality rate is associated with metastasis.[8-10]

It has been reported that tumor progression and metastasis associate with epithelial-mesenchymal transition (EMT). This transition altered interaction of cell-cell, cell-extracellular matrix and induce epithelial cell forming mesenchymal phenotype with higher motility.[11] Indeed, EMT occurs in normal development. It is reversible and, in some cases, cells undergo mesenchymal to epithelial transition (MET). In normal development, EMT and MET were highly planned and regulated, whereas in tumorigenesis, the order of mechanism is uncertain, time-independent, or some pathway maybe miss-regulated. During tumorigenesis, molecular program leads to EMT as consequence of oncogenic signaling.[12] EMT is found well correlated with poor prognosis of neoplastic disease. Activation of EMT has been marked as critical process for anomaly and malignant phenotypes of cells. The role of EMT support malignant cell to invades, migrates and metastasis in distant organs.[13] EMT dysregulation is reported found in various malignant cell, like breast, prostate, colon and lung.[14-17]

Transition into mesenchymal or epithelial cell surface polarity is mediated by E-cadherin protein.[12] In association with EMT during tumorigenesis, the expression of E-cadherin is down-regulate, resulting loss of cell-cell adhesion and cell junction and promote malignant cell to invade surrounding tissue and migrate to distant organ.[18] Loss of E-cadherin expression has been reported in many human malignancies.[19-22]

There are several transcription factors, which are involved in the EMT process, and one of them is zinc finger Enhancer Box (E-Box) binding homeobox 1 (ZEB1). ZEB1 promotes EMT through suppressing the cell adhesion protein E-cadherin, which is prominent glycoprotein in controlling the epithelial phenotype.[23] ZEB-1 suppress E-cadherin expression through binding to E-box in the promoter of Cadherin 1 (CDH1) and recruits C-terminal binding protein (CtBP) transcriptional co-repressors, triggering to suppressed CDH1 transcription and promote EMT.[24] It has been reported that up-regulation of ZEB-1 expression plays a role in progression and metastasis in various tumor.[25-27] Among EMT markers, the clinical importance of ZEB1 in PCA has been shown. Indeed, its expression is boosted according to the various progression steps of PCA and is correlated with reduced overall survival. ZEB1 is a key transcription factor for EMT that promotes multi-drugs resistance, proliferation, and metastasis.[28,29]

Association of E-cadherin and ZEB1 as regulator in EMT process has been showed in many studies. In Indonesia, study about this association is still rarely done, especially in prostatic anomaly condition. In this study, we describe a correlation of E-cadherin and ZEB1 expression in prostatic anomaly using Formalin Fixed Paraffin Embedded (FFPE) samples.

Materials and methods

Sample Collection

This was a cross-sectional study which involved 20 patients with prostatic anomaly. Samples were FFP block from Laboratory of Cito Yogyakarta which stored from 2017 until 2018, in collaboration with Anatomical-Pathology Department of Medical Faculty, Universitas Gadjah Mada. Samples were taken purposively regarding prostatic anomaly tissue were difficult to obtained. Detail of subjects

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identity were confidential and not showed in this study. Samples consist of 8 block of BPH, 6 blocks of HGPIN and 6 blocks of PCA. The blocks then sliced into 5 sections to be prepared for RNA extraction procedures. This study was approved by Medical and Health Ethics Comittee of Medical Faculty, Universitas Gadjah Mada (Ref: KE/FK/0888/EC/2018).

Total RNA Extraction and Reverse Transcriptase-PCR (RT-PCR)

Total RNA was extracted from FFPE sections using miRNeasy FFPE Kit (Cat. No. 217504, Qiagen, Hilden Germany). After FFPE blocks were sliced, the sections were placed in safe lock tubes (1.5 mL), and 160 µL Xylene was added to each tube, for deparaffinization process. The RNAs were eluted in 30 µL RNase-free water. RNA concentration and purity was calculated using Nanodrop (NanoVue Plus, GE Healthcare, Life Science, Chicago, IL, USA). The cDNA synthesis was carried out by reverse transcription reactions using miRCURY LNA RT Kit (Cat. No 339340, Qiagen) and ReverTra Ace® qPCR RT Master Mix with gDNA remover (FSQ-301, Toboyo, New York, NY, USA). All the process were performed using thermal cycler (Cat. No. A248111, Applied Biosystems, Waltham, MA, USA) following the manufacturer's guidelines. The cDNA were stored at -20°C until further analysis.

PCR and Electrophoresis of E-Cadherin and ZEB1 mRNA

E-Cadherin (CDH1) and ZEB1 mRNA expression was analyzed by semi-quantitative procedures using PCR and electrophoresis, compared to β-actin expression as housekeeping gene. This study used GoTaq ® Green Master Mix (Promega, Madison, WI, USA). Master Mix as much as 12.5 µL, forward primer 1 µL, reverse primer 1 µL and nuclease free water 9.5 µL were added into 3 µL cDNA template. Annealing temperature for ZEB1 and E-Cadherin were set at 57°C and for β-actin at 56°C, for 40 cycles. Then, followed by electrophoresis procedure in agarose gel 2%, at 100 V for 12 minutes. We used ImageJ software to analyze the intensity of electropherogram bands' densities. The mRNA primer sequences are showed in Table 1.

Data Analysis

Data were analyzed using SPSS 21 (IBM Corporation, Armonk, NY, USA). Subject characteristics were described as mean and standard deviation (minimal and maximal score), or as total number (n) and percentage. Mean difference were analyzed using non-parametric Kruskal-Wallis test. Correlation between ZEB1 and E-Cadherin mRNA expression was analyzed using Spearman's rank correlation. Statistically significant is considered when p-value<0.05.

Results

Subject Characteristic

This study involved 20 subjects of prostatic anomaly, who consist of 8 patients of BPH, 6 patients of HGPIN and 6 patients of PCA. Patient were dominated by elderly with average of age was 68 years old. Relative expression of E-cadherin and ZEB1 in each group of prostatic anomaly were not significantly different (p>0.05). Subject's characteristic was shown in Table 2.

Correlation of ZEB-1 and E-Cadherin mRNA Relative Expression

Based on bivariate correlation analysis, ZEB1 and E-Cadherin mRNA expression showed a significant and moderate level of negative correlation (p<0.05; 0.40 < r < 0.59). This was means that increasing of ZEB1 mRNA expression will be followed by decreasing of E-Cadherin mRNA expression, and *vice versa*. ZEB1 mRNA expression

Table 1. Primer sequence of ZEB1, E-Cadherin and β-actin.

mRNA		Primer Sequences	Product Lenght
ZEB1	*Forward*	5'- CGGCGCAATAACGCTGTTT -3'	166 bp
	Reverse	5'- GTTCTCACACCCCACACCTC-3'	
CDH1	*Forward*	5'- TCATGAGTGTCCCCCGGTAT -3'	240 bp
	Reverse	5'- TCTTGAAGCGATTGCCCCAT -3'	
β-actin	*Forward*	5'-CGCGAGAAGATGACCCAGATC-3'	125 bp
	Reverse	5'-TCACCGGAGTCCATCACGA-3'	

Table 2. Subject characteristic with prostatic anomaly.

Characteristic of Subject	Value (n=20)	*p* -value
Age (years), mean±SD (min–max)	68±11.4 (44–81)	-
Prostatic Anomaly Status, n (%)		-
BPH	8 (40)	
HGPIN	6 (30)	
PCA	6 (30)	
Average of ZEB1 Relative expression, mean±SD (min–max)		0.781[a]
BPH	1.98±0.38 (1.56–2.67)	
HGPIN	2.06±0.35 (1.57–2.58)	
PCA	2.05±0.25 (1.81–2.51)	
Average of E-Cadherin relative expression, mean±SD (min–max)		0.745[a]
BPH	0.62±0.32 (0.13–0.99)	
HGPIN	0.61±0.28 (0.18–0.90)	
PCA	0.72±0.31 (0.24–1.12)	

[a]Independent-samples Kruskal-Wallis test; significant if *p*-value<0.05.

could affect E-Cadherin mRNA expression as much as 30,8% (R^2=0.308). Correlation of ZEB1 and E-Cadherin were shown in Figure 1. Meanwhile, average of ZEB1 and E-Cadherin mRNA expression were shown in Figure 2. Average of ZEB1 mRNA expression was 2.03±0.32 fold, and average of E-Cadherin mRNA expression was 0.65±0.29 fold.

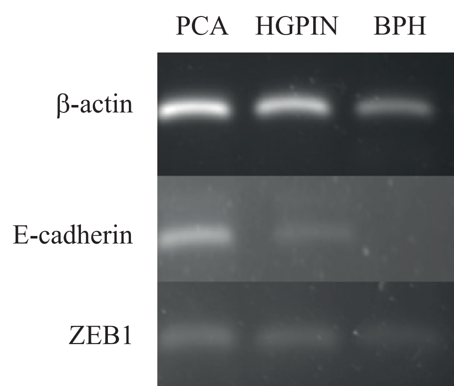

Figure 1. Gel Electrophoresis result of β-Actin (125bp), E-cadherin (240bp), and ZEB1 (166bp).

Discussion

Down-regulation of E-cadherin expression has been studied in many prostatic anomalies.[30,31] In line with current study, E-cadherin expression in BPH, HGPIN and PCA were in suppressed condition. A study using immunostaining on BPH specimen showed a reduced point of tight junction, destabilization of tight junction formation, increased of epithelial permeability, leakage of prostate-specific antigen and other secretory protein from glandular lumen into stromal compartment, as consequence of E-cadherin downregulation.[30] In prostatic intraepithelial neoplasia, lost of E-cadherin expression promote cell apoptosis and interfere epithelial integrity.[31] E-cadherin downregulation is a hallmark of EMT, and equally followed by mesenchymal neural cadherin (N-cadherin) upregulation. This transition induce cells to lose affinity and facilitate cell migration to distant organ.[32] Alteration in normal E-cadherin structure and function resulting abnormal tissue architecture and onset of disease.[33] The role of cell-cell adhesion in the metastasis of cancer has been investigated. To permit extravasation from the primary tumor and subsequent metastasis, the loss of

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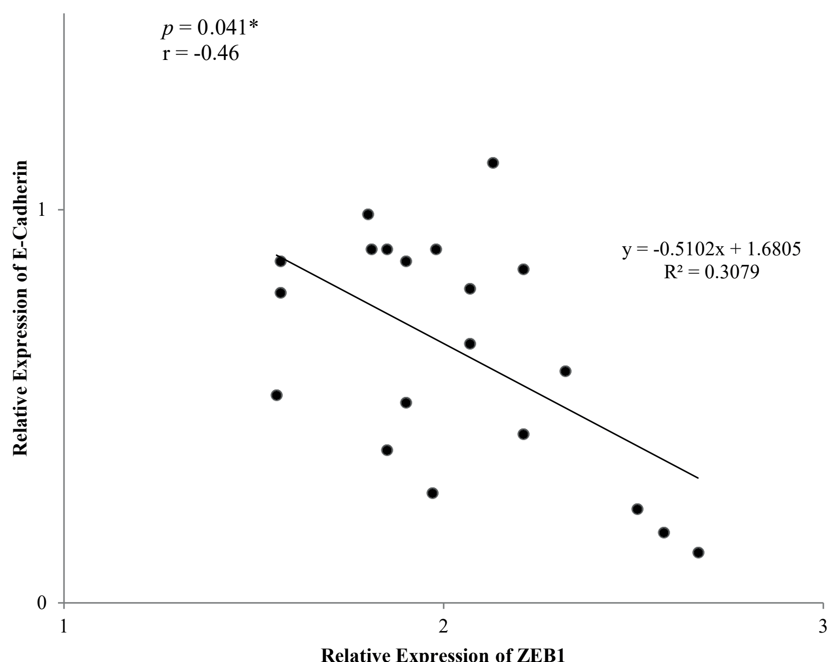

Figure 2. Average of ZEB1 and E-Cadherin relative expression in prostatic anomaly.

cell-cell adhesion is essential, and the loss of cell adhesion molecules has been associated with cancer progression.[10]

E-cadherin is a transmembrane protein that plays a key role in migration and cell adhesion. The β-catenin/APC pathway, which relates to cell proliferation and EMT, also involves E-cadherin. E-cadherin deficiency is associated with poor prognosis for all human patients with high-grade prostate tumors. E-cadherin downregulation in human medicine has been associated with numerous mechanisms, including copy number loss, somatic mutations, methylation, and inhibition mediated by ZEB1 and SRC family kinases.[22,34]

During EMT process, E-cadherin expression in transcriptional level is repressed by nuclear factor (E-cadherin transcriptional repressors, EcTRs) such as ZEB1. ZEB1 binds to E-box sequences of E-cadherin promoter region to suppress E-cadherin transcription.[32] ZEB1 has high specificity binding to E-box sequences of E-cadherin promoter region due to its helix-loop-helix motif. This motif is commonly found in transcription factors that bind DNA.[29] ZEB1 as transcription factors can induce this epithelial-to-mesenchymal switch.[10]

This result study was in line with previous study that E-cadherin and ZEB1 expression is negatively correlates. An *in vitro* study of prostate cancer cells revealed that ZEB1 plays an important role for transendhotelial migration of prostate cancer cell line. Many of epithelial genes, including E-cadherin, were downregulate in condition of ZEB1 highly expressed. On contrary, in ZEB1 silenced cells, E-cadherin expression is highly expressed. This condition promotes migration and invasion of tumor-stroma interface.[27] Loss of E-cadherin and up-regulated ZEB1 expression has been associated with poor clinical condition in many malignancies, including prostate cancer. High expression of ZEB1 is associated with high Gleason score in prostate adenocarcinomas, and promotes aggressive phenotype in prostate cancer cell.[35,36] Recent studies showed that upregulation of ZEB1 induces chemoresistance due to enhanced DNA damage response and DNA repair ability.[37] Moreover, downregulation of E-cadherin expression from paraffin-embedded tumor tissue sample of patients with localized prostate cancer associated with recurrence of prostate cancer after one-year post-surgical.[38]

Limitation of this study was obtained in small sample size of patient with prostatic anomaly. However, our study provides more insight about correlation of E-cadherin and ZEB1 expression in BPH, HGPIN and PCA paraffin-embedded tissue samples, especially in Indonesian patients.

Conclusion

In conclusion, our research has shown that ZEB1 is negatively correlate with E-cadherin mRNA expression due to EMT process in prostatic anomaly. High expression

of ZEB1 induced down-regulation of E-cadherin in BPH, HGPIN and PCA patients. This result may suggest an appropriate therapeutic target to prevent severity of illness and minimize the side effect of therapies. Various studies can be developed, especially the development of targeted therapy against ZEB1 to suppress the EMT process by increasing the expression of E-cadherin.

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