UNIVERSITI PUTRA MALAYSIA

CORRELATION BETWEEN HPV INFECTION AND HUMAN BETA-DEFENSIN mRNA EXPRESSION IN PTERYGIUM AND NORMAL CONJUNCTIVA EPITHELIAL CELLS

ABUBAKAR SAADATU ALIYU

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By

ABUBAKAR SAADATU ALIYU

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Master of Science

November 2017

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DEDICATION

I would like to dedicate this thesis to my parents who have supported me with prayers since before I was born. Also, this thesis is dedicated to my beloved son and the entire humanity who believe in knowledge.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science

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Chairman : Associate Professor Muhammad Hj Mohd Isa,
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Pterygium is a wing-shaped fibro-vascular proliferative lesion that originates from the bulbar conjunctiva and spreads to the corneal limbus and beyond.They are often seen on the nasal side horizontally in the interpalpebral fissure, but may appear on temporal sides too. It is known to cause irregular astigmatism which can compromise vision, corneal scarring, and restriction of ocular motility or ocular surface inflammation. Human β-defensins (HBDs) and viral oncogene such as human papillomavirus (HPV) may be involved in its etiology and development which are still a matter of contention. The aim of this study is to establish the relationship between HPV infection and human β-defensins mRNA gene expression in pterygium. Thirty pterygium and 30 normal conjunctiva epithelial samples were used in the study. Genomic DNA extracted from pterygium and normal conjunctiva was used to determine HPV-DNA using consensus general primer (GP5+/6+) by real time-PCR assay. Subsequently, HPV specific type 16 and 18 primers were used in HPV infected samples for subtyping. Human β -defensins DEFB1, DEFB4A, and DEFB109 mRNA expression were evaluated using real-time PCR and ΔΔ-Ct method was used to calculate relative quantification of human beta defensins (HBDs) in Pterygium and normal conjunctiva epithelial cells. The relationship between HPV infection and human beta- defensins was analysed by Spearman's non parametric correlations for each bivariate pair. HPV viral DNA was detected in 29 of 30 Pterygium and 10 of 30 normal conjunctiva samples respectively, HPV 18 was the most common viral type identified. The expression of human β -defnsins DEFB1 and DEFB4A were up-regulated in pterygium when compared with that of normal conjunctiva of the same patient, while no significant difference was observed in DEFB4A expression. However, the expression of DEFB109 was significantly down- regulated in pterygium compared to that of normal conjunctiva.

Finally, there was positive correlation in DEFB1 and DEFB4A expression with HPV infection in normal conjunctiva epithelial cells. The current data suggest that HPV and HBDs may play a crucial role in pterygial development thus, may be considered as novel molecular target in understanding pterygium pathogenesis.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

KORELASI ANTARA KADAR JANGKITAN HPV DAN EKSPRESI HUMAN BETA-DEFENSIN mRNA DI DALAM PTERYGIUM DAN SEL EPITHELIAL KONJUNKTIVA YANG NORMAL

Oleh

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Pengerusi : Profesor Madya Hj Muhammad Hj Mohd Isa, MD
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Pterigium merupakan lesi proliferatif vaskular fiber berbentuk sayap yang berpunca dari konjunktiva bulbus dan merebak ke limbus kornea dan sebaliknya. Lesi ini juga sering dilihat di bahagian nasal selari dengan interpalpebral fisur, atau dibahagian nasal dan temporal, ia boleh menyebabkan astikmatime tidak tetap yang boleh menjejaskan penglihatan, kornea berparut, kekangan pergerakan okular atau radang permukaan okular. Human beta-defensins (HDBs) dan virus onkogen seperti HPV mungkin bertindak sebagai etiologi yang masih belum diketahui. Tujuan penyelidikan ini adalah untuk mengkaji korelasi antara kadar jangkitan HPV dengan ekspresi gen mRNA HBDs dalam pterigium. Sebanyak 30 sampel pterigium dan 30 sampel epitelial konjunktiva normal telah digunakan dalam kajian ini. Genomik DNA yang diekstrak daripada sampel-sampel tersebut digunakan dalam pengesanan DNA HPV mengunakan RT-qPCR. Primer umum (GP5+/6+) digunakan untuk mengesan HPV, kemudian primer jenis spesifik HPV 16 dan 18 digunakan untuk menentukan subtyping bagi sampel HPV-positif. Ekspresi mRNA HBDs DEFB1, DEFB4A dan DEFB109 telah dinilai menggunakan RT-qPCR and kaedah ΔΔ-Ct digunakan untuk mengira pengkuantitian relatif ekspresi gen HDBs dalam pterigium dan sel epithelial konjunktiva normal. Hubungan antara kadar jangkitan HPV dan ekspresi HBDs telah diuji menggunakan analisis. Genom HPV dikesan dalam 29 sampel pterigium dan 10 sampel konjunktiva normal, HPV 18 merupakan serotaip virus yang paling banyak dikesan. Ekspresi HDBs DEB1 dan DEFB4A adalah tinggi dalam pterigium apabila dibandingkan dengan sel epithelial konjunktiva normal dari pesakit yang sama walaupun ekspresi DEFB4A tidak menunjukkan perbezaan yang ketara secara statistik. Manakala ekspresi DEFB109 adalah rendah dalam secara ketara dalam pterigium berbanding dengan konjunktiva normal.

Secara keseluruhannya, kajian ini menunjukkan korelasi positif antara ekspresi DEB1 dan DEFB4A dengan jangkitan HPV dalam sel epithelial konjunktiva normal. Kajian ini juga menunjukkan bahawa HPV dan HBDs mungkin berperanan penting dalam patogenesis pterigium, dan boleh dijadikan target molekular dalam kajian lanjutan mengenai pterigium.

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This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

ADP	Adenosine 5'-diphosphate
AD	Transactivation domain
APC	Antigen Presenting Cell
AP1	Activator Protein 1
BD	Bond distance
Bp	Base pair
BP	Base peak
C	Carbon
CIN	Chromosomal instability
CBP	CREB-binding protein
CD4+	
CREB	Cyclic AMP response element-binding protein
COX-2	Cyclooxygenase 2
DHA	Hydrogen donor; hydrogen; hydrogen acceptor
D	Day
DC	Dendritic cells
Dntp	Deoxynucleotide triphosphates
DBD	DNA binding domain
DNA	Deoxyribonucleic acid
EGFR	Epidermal growth factor receptor
ECM	Extracellular matrix
EBV	Epstein-Barr Virus
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor

ERK	Extracellular signal-regulated kinase
FPRL1	Formyl peptide receptor-like 1
ERK	Extracellular signal-regulated kinase
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
Bfgf	Growth factors
H_2O	Water
HB	Hydrogen bond
HBD	Human β-defensin
HB-EGF	Heparin-binding epidermal growth factor
HCAP18	Human cationic anti-microbial protein 18
HD	Human defensin (epithelial-derived human α-defensin)
HIF-1α	Hypoxia inducible factor 1α
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HNP	Human neutrophil peptide (neutrophil-derived human α-
HBDs	Human beta-defensins
HDM2	Human double minute 2
HPV	Human papillomavirus
Hogg1	Human 8-oxoguanine DNA glycosylase 1
HSV	Herpes simplex virus
IARC	International agency for cancer research
IU	International unit
IL-1β	Interleukin 1β116
IFN-γ	Interferon γ
IκB	Inhibitor of Kb
PS3	Integrin alpha-

ICTV	International Committee on the Taxonomy of Viruses
L	Litre
LOH	Loss of heterozygosity
LTA	Lipoteichoic acid
LPS	Lipopolysaccharide
MAGUK	Membrane associated guanalyte kinase
mg/Ml	Milligrams per millilitre
Min	Minute
MMP7	Metalloproteinase-7
m.p	Melting point
Mg	Milligrams
MDM2	Murine double minute 2
MAPK	Mitogen-activated protein kinase
MMC	Mitomycin C
MMPs	Matrix metalloproteinases
SMA	Spinalmuscular atrophy
SMN	Survival motor neuron
Mrna	Messenger RNA
NDP	Nucleoside diphosphates
NF-Kb	Nuclear Factor kappa B
NLS	Nuclear localisation signal
NF-Kb	Nuclear factor Kb
NK cells	Natural killer cells
O	Oxygen
ODC	Ornithine decarboxylase
OSCC	Oral squamous cell carcinoma

PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
PMA	Phorbol 12-myristate 13-acetate
p53	Tumour suppressor
RNA	Ribonucleic acid
RPs	Ribosomal proteins
Rpm	Revolutions per minute
RT-PCR	Real- time-polymerase chain reaction
S	Second
SCCHN	Squamous cell carcinoma of the head and neck
SCID	Severe combined immunodeficiency
STAT	Signal transducer and activator of transcription
TAM	Tumour associated macrophage
TGFα	Transforming growth factor α: Ligand to EGFR receptor
TNFα	Tumor necrosis factor α
TNM:	A clinical staging system for grading SCCHN tumours: (T: refers to tumour size at the primary tumour site, N: refers to the status of cervical lymph nodes, and M: refers to the presence or absence of distant metastases)
TBP	TATA binding protein
TIL	Tumor infiltrating lymphocytes
TLR	Toll-like receptor
T	Triplets
UVR	Ultraviolet radiation
Vwf	von Willebrand factor
VLP	virus-like particles
WHO	World Health Organisation

%	Percent
°C	Degree Celsius
µg/Ml	Microgram per millilitre
µM	Micro molar
µL	Micro litre
>	Greater than
A	Alpha
β	Beta

CHAPTER 1

INTRODUCTION

1.1 Research Background

Pterygium is a wing-shaped fibro vascular proliferative lesion that originates from the bulbar conjunctiva, which spreads to the corneal limbus and beyond. They are often seen on the nasal conjunctiva in the interpalpebral fissure although they can appear either or on both the nasal and temporal sides (Masters and Harris 2015). The prevalence rate of pterygium as reported in different studies varies widely with age, gender and geographical location. They are mostly observed in people from tropical climates, but pterygium can be found in over 200 million people worldwide (Lucas et al. 2008). The exact aetiology of pterygium is not fully understood. Previous studies suggested that pterygium was highly associated with ultraviolet radiation (UVR) exposure. Molecular alterations associated with pterygium include loss of heterozygosity (LOH), point mutations of proto-oncogenes (K-ras) and alterations in the expression of tumour suppressor genes (p53 or p63) and nuclear factor (cyclic AMP response element-binding protein CREB) (Nubile et al. 2013). Other findings in pterygium include the frequent detection of HPV DNA, over expression of various ocular surface proteins, including defensins and phospolipases D, as well as the up-regulation of growth factors, such as bFGF or VEGF (Detorakis and Spandidos 2009).

Pterygium can cause irregular corneal astigmatism, corneal scarring and restriction of ocular motility. In some severe cases, pterygium may result in visual impairment if it approaches visual axis or chronic ocular surface inflammation (Liu et al. 2013; Julio et al. 2013). Traditionally, pterygium is regarded as a disease of the elderly, leading to suspicion of primary degenerative cause. Pterygium management usually depends on the size and extent of the pterygium. A small pterygium can be treated with mild steroid eye drops (Rachmiel, Leiba, and Levartovsky 1995) while a large size would require surgery (Bozkir, Yilmaz, and Maden 2008; Ozkurt et al. 2009; Varssano et al. 2013) which is normally enhanced by the use of antimetabolites. Recent progress in the biochemical and molecular pathogenesis of pterygium in recent years has helped in the use of minimally invasive methods of treatment like minimally invasive pterygium excision MIPE (Bozkir, Yilmaz, and Maden 2008).

The pathological mechanism that causes pterygium appears to be multi factorial as the exact mechanism has yet to be elucidated (Chalkia, Spandidos, and Detorakis 2015). Several theories have been put forward to clarify how pterygium progresses include; autosomal dominant mode of inheritance, immunologically-mediated, tear film disruptions, chronic UVR exposure, and viral infection (Di Girolamo 2012).

Human papillomavirus (HPV) are small double-stranded circular DNA non-enveloped viruses with genome size of approximately 8000 bp, encoding early-region sequences or open-reading frames (ORF) designated as E1–E8 that vary in number between HPV types and are expressed shortly after HPV infection. The viral genome also contains two latent regions labeled L1 and L2, which encode the capsid protein that has a role in viral entry. There are over 200 different types of HPV identified but not all have been characterized as oncogenic virus (Di Girolamo 2012). HPV viruses can infect stratified squamous mucosal, cutaneous, and other epithelia cells of mammals. They are found to be associated with squamo-proliferative lesions of the anogenital region, skin and oropharynx. Several studies have shown HPV involvement in the pathogenesis of conjunctival neoplastic lesions, including papilloma and squamous cell carcinoma (Chalkia, Spandidos, and Detorakis 2015). The involvement of HPV as a co-factor in the pathogenesis of pterygium, suggested by several studies using PCR and immunehistochemical techniques, remains controversial. Moreover, a marked variation in the prevalence of HPV in ophthalmic pterygium has been reported by several studies. The HPV infection rate was found to be high as 50-100% pterygium in some studies (Detorakis, Drakonaki, and Spandidos 2000; Di Girolamo 2012; Chalkia, Spandidos, and Detorakis 2013; Chalkia, Spandidos, and Detorakis 2015) but was unable to be detected in other studies (Schellini et al. 2006; Sjö et al. 2007; Hsiao et al. 2010; Masters and Harris 2015).

Defensin family consists of small (2-6 kDa) cationic antimicrobial peptides between 20-50 amino acids with six evolutionary conserved cysteine residues (Liu et al. 1997). They form disulphide bridges in three pairs, giving rise to three anti-parallel beta sheets structure that assume evolutionary conserved structural fold (Jia et al. 2001; Ganz 2003). Apart from the six cysteine residues, members of the defensin family have low sequence homology. This observation was believed to result in the difference of characters between all the family members. In humans, 6 α-defensins and 11 human β-defensins have been isolated (Zhou et al. 2013). Human β-defensins (HBDs) are produced by epithelial cells lining the body surface and acts as natural antibiotics and immunoregulators thus, providing the first line of defence against infection, inflammation and wound healing (Zhou et al. 2013). HBDs have wide-spectrum of antimicrobial and biological activities with little risk of developing resistances. They can also inhibit many steps in viral infection as well as growth of microbes (Wilson, Wiens, and Smith 2013). The expression of human β-defensins is either constitutive or inducible in response to infection or tissue injury (Dhople, Krukemeyer, and Ramamoorthy 2006; Wehkamp et al. 2007). When induced they normally result in their most effective site-specific response.

Human β-defensins (hBDs) demonstrate proinflammatory activity by binding to certain receptors. For example, human β-defensin 2 (hBD-2) and human β-defensin 1 (hBD1) bind to chemokine receptor 6 (CCR6) leading to increment in chemo-attraction of both CD4+ memory T-helper cells and immature dendritic cells (Yang et al. 1999). hBDs can also play a role in cancinogenesis of epithelial tumours. Changes in expression of human β-defensins was observed in epithelial-derived cancers such as prostatic cancer, basal cell carcinoma, oral squamous cell carcinoma (OSCC) and renal cell carcinoma (Al-Rayahi and Sanyi 2015). The variation in expression pattern

of β-defensins in such cancers has led researchers to investigate anti-tumour potential of β-defensins.

1.2 Problem Statement

The pathogenesis of pterygium is not fully understood and several factors have been implicated in the formation of pterygium. Central to these factors are the ultra violet ray (UVR) damage while the role of oncogenic viral infection is controversial. The presence of Human papillomavirus (HPV) in patients diagnosed with pterygium was found to be as high as 50-100% in several studies but failed to be detected in other studies. Insertion of HPV 16/18 DNA into the host chromosome to express the E6/E7 oncoprotein plays crucial roles in HPV-induced cervival carcinogenesis. Human β-defensin is produced by the epithelial cells lining the body surface, thus providing immediate and direct response towards external challenges. Defensins play important role in the innate immunity and adaptive immunity. They protect the host by conferring first line protection against invading organisms such as bacteria, fungi and viruses. In addition to the antimicrobial role, defensins are involved in various cellular processes such as chemo-attraction, anti-cancer function wound healing and cell proliferation. Based on these functions of the defensins and given the events underlying the pathogenesis of pterygium, HPV and human β-defensins may influence the pathogenesis of pterygium. However, the relationship between them has not been established and become the focus of this study.

1.3 Research Questions

1. Is the HPV infection significantly increased in pterygium than in normal conjunctiva?
2. Is the human beta-defensins genes up- regulated or down-regulated in pterygium compared to that of normal conjunctiva?
3. What is the correlation between the human beta defensins gene and HPV infection rate in pterygium?

1.4 General Objective

The aim of this study was to determine the correlation between Human Papillomavirus (HPV) infection and Human β-defensin mRNA gene expression using real time Polymerase Chain Reaction (qPCR) in pterygium and normal conjunctival epithelial cells from patients undergoing the pterygium excision.

1.4.1 Specific Objectives

1. To determine the prevalence of human papillomavirus infection in pterygium and normal conjunctiva epithelial samples.
2. To determine high-risk human papillomavirus HPV-16 and HPV-18 in HPV infected pterygium and normal conjunctiva samples.
3. To determine DEFB1, DEFB4A, and DEFB109 mRNA expression in pterygium and normal conjunctiva epithelial samples.
4. To determine the correlation between the HPV infection and the human β-defensins gene expression in pterygium and normal conjunctiva samples.

1.5 Research Hypotheses

i. The HPV infection will increase in pterygium compared to normal conjunctiva samples.
ii. The human β-defensins gene expression will reduce in pterygium compared to normal conjunctiva samples.
iii. Down regulation of human β-defensin mRNA expression would increase the risk of HPV infection in pterygium.

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