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AIRWAY REMODELING BLOCKADE WITH AN ORALLY ACTIVE GERANYL ACETOPHENONE

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By

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AIRWAY REMODELING BLOCKADE WITH AN ORALLY ACTIVE GERANYL ACETOPHENONE

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Chair: Professor Daud Ahmad Israf Ali, PhD
Faculty: Medicine and Health Sciences

In the last few decades, structural changes of airways in asthma has gained huge attention from both clinicians and scientists as current therapeutic approaches are inadequate in attenuating airway remodeling, especially in severe asthma patients. Airway remodeling includes subepithelial fibrosis, thickening of basement membrane, hyperplasia and metaplasia of epithelial and goblet cells, mucosal gland enlargement and increase in smooth muscle mass with loss of lung function. Current asthma treatment with corticosteroids that suppress lung inflammation and bronchodilators which ease breathing difficulties have limited effect on airway remodeling. In addition, there are 10% of patients do not respond to treatment. Moreover, noncompliance in asthma patients to inhaler devices is also a major problem. New intervention is clearly needed to address these issues. 2,4,6-trihydroxy-3-geranyl acetophenone (tHGA) is a synthetic compound naturally found in *Melicope ptelefolia*. Intraperitoneal administration of tHGA is able to reduce lung inflammation in a murine model of acute asthma. In this study, the efficacy of orally administered tHGA upon airway remodeling in a murine model of chronic asthma was evaluated. The mode of action was assessed via model of eosinophil-induced epithelial-mesenchymal transition. A standard 6 week ovalbumin-challenged BALB/c mice model of chronic asthma was used. Oral tHGA treatment was found to attenuate airway hyperresponsiveness and remodeling in a dose-dependent fashion. tHGA's dose of 80 mg/kg per os was found to be most effective while 20 mg/kg did not exert any effect. The deposition of extracellular matrix proteins (collagen I, fibronectin and tenascin C) and hyperplasia of myofibroblasts and smooth muscle cells was also inhibited by tHGA. tHGA's effect on airway remodeling could be attributed to the reduction of inflammatory cell infiltration and decreased expression of

cytokines associated with airway remodeling like interleukin (IL)-4, IL-13 and transforming growth factor (TGF)-β. Epithelial-mesenchymal transition (EMT) is currently recognized as the main cellular event that contributes to airway remodeling. The effect of synthetic 2,4,6-trihydroxy-3-geranyl acetophenone (tHGA) upon eosinophil-induced epithelial-mesenchymal transition in a cellular model was assessed. The human eosinophil cell line EoL-1 was used to induce EMT in BEAS-2B human bronchial epithelial cells. The induction of EMT was dose-dependently suppressed following tHGA treatment in which the epithelial morphology and E-cadherin expression were not altered. Protein and mRNA expression of vimentin, collagen I and fibronectin in eosinophil-induced epithelial cells were also significantly suppressed by tHGA treatment. The protein and gene expression of TGF-β were found to be significantly inhibited by 30 μM tHGA. However, tHGA was incapable of impeding TGF-β-induced EMT in BEAS-2B cells. Following pathway analysis, tHGA was found to suppress eosinophil-induced activator protein-1 (AP-1)-mediated TGF-β production in bronchial epithelial cells by targeting c-Jun N-terminal kinase (JNK) and phosphoinositide 3-kinase (PI3K) signaling pathways. In conclusion, tHGA's effective inhibition on TGF-β production may largely contributed to its capacity in ameliorate airway remodeling. Our findings potentiate the possibility of tHGA's development as a new non-steroidal oral lead for the management of asthma.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
Sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PERENCATAN PEMODELAN SEMULA SALURAN PENAFASAN DENGAN GERANYL ACETOPHENONE YANG AKTIF SECARA ORAL

Oleh

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Pada beberapa dekad yang lalu, perubahan pada struktur saluran pernafasan akibat penyakit asma telah menarik perhatian doktor dan saintis kerana pendekatan terapeutik terkini tidak menunjukkan keberkesanan pada proses pemodelan semula saluran pernafasan terutamanya terhadap pesakit asma yang tenat. Pemodelan semula saluran pernafasan yang merangkumi fibrosis bawah epitelium, penebalan membran epitelium, hiperplasia dan metaplasia epitelium, pertumbuhan sel goblet dan kelenjar mukus serta penambahan jisim otot licin boleh menyebabkan kehilangan fungsi paru-paru. Rawatan semasa dengan kortikosteroid dan bronkodilator amat berkesan untuk mengurangkan keradangan paru-paru dan kesukaran pernafasan. Akan tetapi, ia hanya menunjukkan keberkesanan yang terhad pada proses pemodelan semula saluran pernafasan. Kira-kira sepuluh peratus pesakit asma didapati tidak memberi respon positif kepada rawatan tersebut. Selain daripada itu, ketidakpatuhan pesakit asma terhadap penggunaan inhaler juga merupakan satu masalah yang serius. Dengan itu, perdekatan baru sangat diperlukan untuk menangani isu-isu tersebut. 2,4,6-trihydroxy-3-geranyl acetophenone (tHGA) adalah molekul sintetik yang asalnya ditemui dalam tumbuhan *Melicope ptelefolia*. Suntikan intraperitoneal tHGA telah dibuktikan untuk mengurangkan keradangan paru-paru dalam model asma akut tikus. Dalam kajian ini, keberkesanan oral tHGA pada pemodelan semula saluran pernafasan telah dikaji dengan menggunakan model asma kronik tikus dan sambil mengenalpasti cara tindakannya dengan menggunakan model peralihan epitelium ke mesenchymal (EMT) induksi eosinophil. Model asma kronik standard mencik BALB/c induksi ovalbumin selama 6 minggu telah digunakan. Rawatan oral tHGA didapati mengurangkan hiper-responsi saluran pernafasan dan menyekat pemodelan semula saluran pernafasan

bergantung dos yang diberikan. Dos oral tHGA pada 80 mg/kg adalah paling berkesan manakala dos 20 mg/kg tidak menunjukkan sebarang kesan. Pemendapan protein matriks extracellular (kolagen I, fibronectin dan tenascin C) serta hiperplasia myofibroblast dan sel otot licin direncatkan oleh tHGA. Kesan tHGA terhadap pemodelan semula saluran pernafasan mungkin disebabkan oleh pengurangan penyusupan sel inflamasi dan perencatan expresi sitokine yang berkaitan seperti IL-4, IL-13 dan TGF-β. Proses EMT telah dikenalpasti sebagai kejadian selular utama yang menyumbang kepada permodelan semula saluran penafasan. Keberkesanan tHGA sintetik terhadap EMT yang dirangsang oleh eosinophil telah dikaji. Sel eosinophil, EoL-1 telah digunakan untuk induksi EMT pada sel epithelial bronkial manusia BEAS-2B. tHGA dapat menindas EMT di mana sel epithelial dapat mengekalkan morfologi epitelium dan penandanya e-cadherin. Tahap protein dan mRNA vimentin, kolagen dan fibronectin pada sel epitelium yang melalui EMT juga dikurang secara ketara oleh tHGA. Protein dan mRNA TGF-β juga dihalang sintesisnya dengan signifikan oleh 30 μM tHGA. Walau bagaimanapun, tHGA tidak dapat menggendalakan EMT induksi TGF-β pada sel BEAS-2B. Penyiasiatan laluan isyarat sel selanjutnya mendapati bahawa tHGA merencat aktiviti AP-1 yang terlibat dalam produksi TGF-β melalui pengganggguan laluan isyarat JNK dan PI3K/AKT. Kesimpulannya, keberkesanan tHGA untuk menghindari produksi TGF-β menyumbang besar kepada keupayaannya dalam perencatan pemodelan semula saluran pernafasan. Hasil kajian ini mempotensikan perkembangan tHGA sebagai rawatan oral baru bukan steroid untuk penyakit asma.

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I certify that a Thesis Examination Committee has met on 12 September 2017 to conduct the final examination of Lee Yu Zhao on his thesis entitled "Airway Remodeling Blockade with an Orally Active Geranyl Acetophenone" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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LIST OF ABBREVIATIONS

AHR	airway hyperresponsiveness
AKT	protein kinase B
AP-1	activator protein 1
ASM	airway smooth muscle
BA	sodium n-butyrate
BAL	bronchoalveolar lavage
BMP	bone morphogenetic protein
BSA	bovine serum albumin
CCL	chemokine (C-C motif) ligand
Cdyn	dynamic compliance
COX	cyclooxygenase
CTGF	connective tissue growth factor
CysLT	cysteinyl leukotriene
DAB	3,3-diaminobenzidine
ddH_2O	deionized water
DMEM	Dulbecco's modified eagle medium
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
ECM	extracellular matrix
EDTA	ethylenediaminetetraacetic acid
EGF	epidermal growth factor
ELISA	enzyme-linked immunosorbent assay

EMSA	electrophoretic mobility shift assay
EMT	epithelial-mesenchymal transition
EMTU	epithelial-mesenchymal trophic unit
ERK	extracellular signal-regulated kinase
FBS	fetal bovine serum
FGF	fibroblast growth factor
GAPDH	glyceraldehyde 3-phosphate dehydrogenase
gDNA	genomic deoxyribonucleic acid
GINA	global initiative for asthma
GM-CSF	granulocyte-macrophage colony-stimulating factor
GSK	glycogen synthase kinase
H&E	hematoxylin and eosin
HDM	house dust mites
HGF	hepatocyte growth factor
HRP	horseradish peroxidase
ICS	inhaled corticosteroids
Ig	immunoglobulin
IGF	insulin-like growth factors
IHC	Immunohistochemistry
IL	interleukin
JNK	c-Jun N-terminal kinases
LIGHT	tumor necrosis factor super family 14

LOX	lipoxygenases
MAPK	mitogen-activated protein kinase
MMP	matrix metalloproteinase
MOPS	3-(N-morpholino) propanesulfonic acid
mRNA	messenger ribonucleic acid
MTT	tetrazolium bromide
NaOAc	sodium acetate
OVA	ovalbumin
PAGE	polyacrylamide gel electrophoresis
PAS	periodic acid schiff
PBS	phosphate buffered saline
PDGF	platelet derived growth factors
Penh	enhanced pause
PI3K	phosphoinositide 3-kinase
PPRs	pattern recognition receptors
Ptch	Sonic hedgehog receptor Patched
PVDF	polyvinylidene fluoride
RI	airway resistance
RNA	ribonucleic acid
RPMI	Roswell Park Memorial Institute
rRNA	ribosomal ribonucleic acid
RT-PCR	reverse transcriptase-polymerase chain reaction
S.E.M.	standard error of mean

SDS	sodium dodecyl sulphate
Shh	Sonic hedgehog
Slug	zinc finger protein SNAI2
SMO	smoothened protein
Snail	zinc finger protein SNAI1
TBE	Tris/borate/EDTA
TBS	Tris buffered saline
TdT	terminal deoxynucleotidyl transferase
TEMED	tetramethylethylenediamine
TGF	transforming growth factor
Th2	T-helper cells 2
tHGA	2,4,6-trihydroxy-3-geranyl acetophenone
TIMP	inhibitor of metalloproteinase
TLR	toll-like receptor
TNF	tumor necrosis factor
TSLP	thymic stromal lymphopoietin
VEGF	vascular endothelial growth factor
ZEB	zebra transcription factor
α-SMA	α-smooth muscle actin

CHAPTER 1

INTRODUCTION

Asthma is characterized as a chronic respiratory disease involving airway inflammation and hyperresponsiveness (AHR) (Barnes, 2008). Common symptoms include wheezing, shortness of breath, coughing and chest tightness (GINA, 2016). It is estimated in year 2014 that more than 334 million people worldwide suffer from asthma (Barnes, 2010; Global Asthma Network, 2014) with high prevalence amongst children (Pedersen et al., 2011) and contributes to 250000 death annually (GINA, 2016). The number of asthma patients is expected to increase to 400 million by year 2025 (GINA, 2016). Global economic costs of asthma has surpassed the cost of tuberculosis and AIDS combined with a staggering annual cost of US$ 12 billion and US$ 22 billion in America and Europe respectively (Braman, 2006).

Just about 30 years ago, the loss of lung function in severe asthma had been attributed to structural changes in the airway termed airway remodeling (Wenzel, 2003). Airway remodeling refers to structural changes in and surrounding the airways including trachea, bronchi and bronchioles during asthma (Tang et al., 2006). Airway remodeling encompasses compromised epithelial integrity (Naylor, 1962), thickening of basement membrane (Roche et al., 1989), subepithelial fibrosis (Elias et al., 1999), goblet cell hyperplasia (Aikawa et al., 1992), increased smooth muscle mass (Carroll et al., 1993), and increased lung vascularity (Tanaka et al., 2003). Transforming growth factor (TGF)-β protein and gene expression in asthmatic patients is upregulated and correlated with asthma severity (Minshall et al., 1997). TGF-β was found to exhibit diverse effects in asthmatic lungs that are associated with airway remodeling (Makinde et al., 2007). Epithelial to mesenchymal transition (EMT) is currently recognized as a source for migrating mesenchymal cells (myofibroblast and fibroblast) that promote subepithelial fibrosis and extracellular matrix (ECM) deposition (Hackett, 2012; Pain et al., 2014). TGF-β is the most potent and well investigated EMT inducer in asthma and normal epithelia (Ijaz et al., 2014; Pain et al., 2014; Xu et al., 2009).

Recent studies have suggested corticosteroids, the gold standard in asthma treatment, as being ineffective in reversing airway structural changes (Doerner and Zuraw, 2009; Royce and Tang, 2009). Moreover, in severe asthma patients, AHR is not abrogated subsequent to corticosteroid treatment (Baraket et al., 2012) as supported by several earlier pioneering studies (Juniper et al., 1990; Lundgren et al., 1988). Corticosteroid treatment was found to be ineffective in suppressing TGF-β and collagen expression in patients (Chakir et al., 2003). Currently, there are no targeted therapies for reversing airway structural

changes in asthma (Olin and Wechsler, 2014; Pascual and Peters, 2005; Yilmaz and Yuksel, 2016). Moreover, noncompliance in asthma patients with inhaler devices is also a problem as patients are concerned about the side effects of corticosteroids (Dinwiddie and Müller, 2002) and patients' preference for an oral treatment (Weinberg and Naya, 2000). A new intervention is clearly needed to address these issues.

The geranyl acetophenone, 2,4,6-trihydroxy-3-geranyl acetophenone (tHGA), contains a bioactive principle of the phloroglucinol structure-core (Shaari et al., 2006). The acylphloroglucinol group naturally found in many natural products exhibits many interesting biological properties (Chung, 1995). Earlier studies revealed that tHGA was able to exert a dose-dependent inhibition of 5-lipoxygenase (5-LOX), cyclooxygenase (COX) activity and cysteinyl leukotriene (CysLT) secretion in LPS-induced macrophage cell lines (Shaari et al., 2011). Further studies demonstrated synthetic tHGA exerted a dose-dependent inhibitory effect upon allergic airway inflammation in ovalbumin (OVA)-induced BALB/c mice following intraperitoneal administration (Ismail et al., 2012).

We hypothetized that tHGA is orally active and able to attenuate airway remodeling in a murine model of chronic asthma through the regulation of TGF-β expression. In this study, the effect of orally administered synthetic tHGA in attenuating airway remodeling in a chronic murine model of asthma was examined. The mechanism of action of tHGA upon airway remodeling was studied in a model of eosinophil-induced EMT followed by pathway disruption analysis to determine the exact molecular target involved.

1.1 Problem statement

This project aims to evaluate tHGA's potential as an orally active drug lead for airway remodeling treatment and to explain tHGA's mechanism of action. This study may addresses the problem of non-complicance of inhaler-based treatment delivery and the ineffectiveness of corticosteroids in treating airway remodeling.

1.2 General objective

To determine the effects and mechanism of action of tHGA on attenuating airway remodeling.

1.3 Specific objectives

i. To determine the effect of orally administered tHGA on airway inflammation and remodeling in a chronic murine model of allergic asthma

ii. To determine the effect of tHGA on eosinophilic cell line, EoL-1 and TGF-β-induced epithelial-mesenchymal transition in normal bronchial epithelial cell, BEAS-2B

iii. To determine the effect of tHGA on EoL-1 coculture-induced TGF-β production in BEAS-2B cells

iv. To explain the inhibitory effect of tHGA on EoL-1-induced EMT via determination of potential pathways affected by tHGA that are involved in TGF-β production

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