Biomechanical Regulation of Endothelial Phenotype

Lee, Ee Soo

Appendices

Acknowledgements

In 2009, right before the completion of my Master degree, I participated in the International Student Congress of (Bio)Medical Science (ISCOMS) Research Fellowships where I met Professor Han Moshage and Professor Marco Harmsen. This acquaintance was a turning point in my life and set my path of research. I was offered a scholarship to pursue a PhD degree in Cardiovascular Regenerative Medicine Research Group (CAVAREM) led by Marco Harmsen. I was very enthusiastic to start my new research on mechanotransduction in endothelial cells in this nascent research group. The joy of learning new things and materialising my dreams (to study and to do research abroad) brought me to a state of euphoria. I enjoyed this fantastic period very much, though I knew the journey ahead in a foreign country and investigating a completely unfamiliar subject is not a piece of cake. After this euphoria, I experienced unexpected and drastic challenges in both my life and research. I am really grateful that in the end of the PhD training, I managed to overcome certain tough challenges and to find a satisfying answer for some life- and research-related questions. I am glad and proud that my quest of life and science in the West ends with lots of enjoyment and achievement (both personal and research). At this moment, I know I had made a right decision to pursue a PhD degree in Groningen. Most importantly, this intense doctoral training opens my eyes to what really matters to science and to me. There are several people whom I really grateful to, for they help to make my challenging doctoral training and thesis compilation fulfilling and enjoyable. I am uncertain if they knew it or not, they have either directly or indirectly supported, helped and inspired me to grow as a better scientist and a better person. They are special and important to me. Therefore, I wish to write a few words about them as a token of my appreciation.

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food and treating me like a family member. I cherish the moment of cooking, making bread, as well as celebrating Christmas and New Year with them. I am also grateful to them for helping me to adapt to the Dutch culture. I would like to express my gratitude to Emmy and her family for their kindness and wonderful Vietnamese-Chinese food. I appreciate the good chat and wonderful Chinese New Year celebration with them. Their way of living a simple, yet happy life inspires me a lot. I would like to thank Gulbahar and her family for their generosity and tasty Turkish food. Their hospitality makes me feel myself at home. I am grateful to uncle HK for his warm and caring character, as well as his awesome Hong Kong-Chinese cuisine. My big thank you to my wonderful housemates and friends, Felipe and Victoria for making my early life in Groningen brighter, warmer and more colourful. My earnest gratitude goes to Kah Keng, Yat Yuen, Mei Chee and Lu Ping for their support from far, as well as for sharing thought on research and survival skills of doing PhD abroad. My special thanks to Adai for sharing the tips for thesis compilation and publication.

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About the Author

Ee Soo Lee received Scholarship for Undergraduate Study from the Public Service Department of Malaysia and started her undergraduate study at the University of Malaya, Malaysia in 2003. She did her undergraduate research project with Dr Adawiyah Suriza binti Shuib and Dr Puteri Shafinaz Akmar binti Abdul Rahman at Professor Onn bin Haji Hashim's lab. Her works on the application of chempedak (*Artocarpus integer*) lectin in glycoproteomic profiling of human serum was compiled for a Bachelor's degree thesis. In 2006, she obtained her Bachelor of Science (Honours) degree in biochemistry at the University of Malaya. She then worked on molecular genetics of lymphoma and nasopharyngeal carcinoma as a research assistant with Professor Suat Cheng Peh at the University of Malaya from 2006 to 2009. She investigated the alteration of *p53* and retinoblastoma-related (*Rb2/p130*) genes in nasopharyngeal carcinoma, in collaboration with Dr. Alan Soo Beng Khoo and his group in Cancer Research Centre, Institute for Medical Research, Malaysia. In 2007, she received Scholarship for Postgraduate Study from the University of Malaya to pursue her research on the alteration of *p16* tumour suppressor gene in diffuse large B-cell lymphoma with Professor Suat Cheng Peh and Professor Wan Ariffin bin Abdullah. In 2010, she obtained her Master of Medical Science degree at the University of Malaya.

Ee Soo is a recipient of an International Student Congress of (Bio)Medical Sciences Research Fellowship (2009) from University Medical Center Groningen, The Netherland during which she was attached to a research group that investigates apoptosis and inflammation of the liver and gastrointestinal tract, led by Professor Han Moshage. She also received a Dr Ranjeet Bhagwan Singh National Fellowship from Ministry of Science, Technology and Innovation, Academy of Sciences Malaysia and the International Medical University, Malaysia (2009) for research training. In 2009, Ee Soo acquired an Ubbo Emmius PhD Scholarship from the University of Groningen, The Netherlands and started her PhD training in the Cardiovascular Regenerative Medicine Research Group (CAVAREM) at the University Medical Center Groningen where she examined the biomechanical regulation of endothelial phenotype with Professor Martin Harmsen. During her PhD training in Groningen, Ee Soo was an editor of the W.J. Kolff Institute Newsletter from 2010 to 2013. In 2012, she represented Malaysia in 1st Asia-Europe Students' Forum, organised by the Asia-Europe Foundation and the ASEAN University Network at the University of Groningen. In 2013, she translated a questionnaire entitled "Obstruction and motivation for sports among Paralympic athlete"

from English to Malay for Department of Rehabilitation Medicine, University Medical Center Groningen, National Paralympic Committee, The Netherlands and International Paralympic Committee. Ee Soo was a University ambassador of 17th International Student Congress of (Bio)Medical Sciences (ISCOMS), University of Groningen in 2010. Currently, she is a Postdoctoral research fellow in Professor Carlos Ibanez's lab at the National University of Singapore, Singapore where she is investigating the signalling mechanisms by which the activin receptor-like kinase (ALK)7 regulates catecholamine sensitivity in adipocytes.

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Appendices

List of Publications

Published

Moonen JAJ, **Lee ES**, Schmidt M, Maleszewska M, Koerts JA, Brouwer LA, van Kooten TG, van Luyn MJA, Zeebregts CJ, Krenning G and Harmsen MC. Endothelial-to-mesenchymal transition contributes to fibro-proliferative vascular disease and is modulated by fluid shear stress. *Cardiovascular Research*. 2015;doi:10.1093/cvr/cvv175. [Epub ahead of print].

Lee ES, Kim LH, Abdullah WA and Peh SC. Expression and alteration of *p16* in diffuse large B-cell lymphoma. *Pathobiology.* 2010;77:96–105.

*Hoe SLL, ***Lee ES**, Khoo ASB and Peh SC. *p53* and nasopharyngeal carcinoma: a Malaysian study. *Pathology.* 2009;4:561-565.

*Equal contribution

Hoe SLL, **Lee ES**, Khoo ASB and Peh SC. Lack of *Rb2/p130* genetic alteration in Malaysian nasopharyngeal carcinoma. *Malaysian Journal of Pathology.* 2009;31:53-56.

Submitted

Lee ES, Solé Boldo L, Fernandez BO, Feelisch M and Harmsen MC. Shear stress counteracts the pro-inflammatory effects of oxidative stress and TGF-β on endothelial cells by suppressing the TAK1 pathway.

Lee ES, Solé Boldo L, Brouwer LA and Harmsen MC. Shear stress does not reverse senescence of endothelial cells despite appropriate sensing: implications for ageing-associated cardiovascular disease.

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ACTA2	actin, α2, smooth muscle, aorta
ALK5	activin receptor-like kinase 5
AMPK	AMP-activated protein kinase
ANOVA	analysis of variance
AP-1	activator protein 1
αSMA	α-smooth muscle actin
ATP	adenosine triphosphate
B2M	β-2-microglobulin
BH_4	tetrahydrobioterin
BMP	bone morphogenetic protein
BMPR	bone morphogenetic protein receptor
CBP	cyclic AMP response element-binding protein (CREB)-binding protein
CCL2	chemokine (C-C motif) ligand 2
CDC42	cell division control protein 42 homolog
CDH5	cadherin 5, type 2
CDKN2A	cyclin-dependent kinase inhibitor 2A
Co-SMAD	common mediator small mothers against decapentaplegic
CNN1	calponin
CRP	C-reactive protein
CXCL8	chemokine (C-X-C motif) ligand 8
DCFDA	2',7'-dichloroflorescin diacetate
DMSO	dimethyl sulfoxide
EC	endothelial cells
EMT	epithelial-to-mesenchymal transition
EndMT	endothelial-to-mesenchymal transition
eNOS	endothelial nitric oxide synthase
ERK1/2	extracellular signal-regulated kinases 1 and 2
ERK5	extracellular-signal-regulated kinase 5
et al	*et alii* (and others)
EZH2	enhancer of zeste homolog-2
FAK	focal adhesion kinase
FBS	foetal bovine serum

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FGF	fibroblast growth factor
GAPDH	glyceraldehyde 3-phosphate dehydrogenase
GDF	growth & differentiation factor
GSK-3β	glycogen synthase kinase-3β
GTPases	guanosine triphosphatases
H_2O_2	hydrogen peroxide
HAEC	human aortic endothelial cells
HUVEC	human umbilical vein endothelial cells
ICAM1	intercellular adhesion molecule 1
i.e.	*id est* (that is)
IFN-γ	interferon-γ
IGF-1	insulin-like growth factor 1
IKK	IκB kinase
IL	interleukin
I-SMAD	Inhibitory small mothers against decapentaplegic
JNK	c-Jun NH_2-terminal kinase
KDR	kinase insert domain receptor
KLF	Kruppel-like factor
LPS	lipopolysaccharides
LSS	laminar shear stress
MAPK	mitogen-activated protein kinase
MAP3K	mitogen-activated protein kinase kinase kinase
MCP-1	monocyte chemotactic protein 1
MEF	myocyte enhancer factor
MEK5	Mitogen activated protein kinase kinase
MET	mesenchymal-to-epithelial transition
MIS	Muellerian inhibiting substance
MKK	mitogen-activated protein kinase kinase
MYC	v-myc avian myelocytomatosis viral oncogene homolog
NADPH	nicotinamide adenine dinucleotide phosphate
NFκB	nuclear factor κ-light-chain-enhancer of activated B cell
NO	nitric oxide
NOS	nitric oxide synthase
NRF2	nuclear factor erythroid 2–related factor 2

$O_2^{\bullet-}$	superoxide anions
•OH	hydroxyl radicals
$ONOO^-$	peroxynitrite
PAI-1	plasminogen activator inhibitor type 1
PECAM-1	platelet/endothelial cell adhesion molecule 1
PI3K	phosphatidylinositol-3-OH kinases
PKB	protein kinase B
RNNO	N-nitrosamines
ROS	reactive oxygen species
R-SMAD	receptor-regulated small mothers against decapentaplegic
RSNOs	S-nitrosothiols
RT-PCR	reverse transcription polymerase chain reaction
RXNO	nitroso compound
SASP	senescence-associated secretory phenotype
SBE	small mothers against decapentaplegic binding elements
SELE	selectin E
SEM	standard error of the mean
SSRE	shear stress responsive elements
shERK5	short hairpin construct directed against ERK5
SM22α	smooth muscle 22α
SMAD	small mothers against decapentaplegic
SRF	serum response factor
SUMO	small ubiquitin-like modifier
TAB2	TAK1-binding protein 2
TAGLN	transgelin
TAK1	transforming growth factor-β-activated kinase 1
TβR	transforming growth factor-β receptor
TCE	transforming growth factor- β control elements
TEK	TEK tyrosine kinase
TERT	telomerase reverse transcriptase
THBD	thrombomodulin
TGF-β	transforming growth factor-β
TNF	tumour necrosis factor
TRAF6	tumour necrosis factor receptor-associated factor 6

VCAM1	vascular cell adhesion molecule 1
VE-cadherin	vascular endothelial-cadherin
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
vWF	von Willebrand factor

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