Bioactive lipids as key regulators in atherosclerosis

Bot, M.

List of Abbreviations

ABCA1	ATP-binding cassette, sub-family A, member 1
ACE	angiotensin coverting enzyme
ADAM	a disintegrin and metalloproteinase
Ag	antigen
AMP	adenosine monophosphate
aP2	adipocyte-specific FABP4
APC	antigen presenting cell
ApoE($^{-/-}$)	apolipoprotein E (deficient)
Arg1	arginase 1
ASMA	smooth muscle α-actin
ATX	autotaxin
BM-mφ	bone marrow-derived macrophage
BSA	bovine serum albumin
CBA	cytometric bead array
CCR	CC chemokine receptor
CD40L	CD40 ligand
CFSE	carboxyfluorescein diacetate succinimidyl ester
CMTMR	orange-fluorescent tetramethylrhodamine
ConA	concanavalin A
COX	cyclooxygenase
$cPLA_2$(IVA)	cytoplasmic phospholipase A_2 (type IVA)
Ct	cycle threshold
DAG(K)	diacylglycerol (kinase)
DC	dendritic cell
DHB	2,5-dihydroxybenzoic acid
DMEM	Dulbecco's modified Eagle's medium
DNP	dinitrophenol
dpm	disintegrations per minute
ECM	extracellular matrix
Edg	endothelial differentiation gene
EDTA	ethylenediamoniotetraacetate
EI	electron impact
eNOS	endothelial nitric oxide synthase
ER	endoplasmic reticulum
ERK	extracellular signal-regulated kinase
ESI	electrospray ionisation
ET-1	endothelin-1
eV	electron volt
FABP	fatty acid binding protein
FBS	fetal bovine serum

FcεRI	high-affinity receptor for IgE
FCS	fetal calf serum
FGF	fibroblast growth factor
FTY720	2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride
FTY720-P	phosphorylated FTY720 (active form)
G3P	glycero-3-phosphate
GPAT	glycerophosphate acyltransferase
GPCR	G-protein coupled receptor
GPR	G-protein coupled receptor
HCCA	α-cyano-4-hydroxycinamic acid
HDL	high-density lipoprotein
HL	hepatic lipase
HMGCoA	hydroxymethylglutaryl-coenzyme A
HPRT	hypoxanthine phosphoribosyltransferase
HSP60	heat shock protein 60
ICAM-1	intercellular adhesion molecule 1
i.d.	injected dose
IFN-γ	interferon-γ
Ig	immunoglobulin
IGF-1	insulin-like growth factor-1
IL($^{-/-}$)	interleukin (deficient)
IL-1RA	interleukin-1 receptor antagonist
IMS	imaging mass spectrometry
iNOS	inducible nitric oxide synthase
i.p.	intraperitoneal
iPLA$_2$(VIA)	Ca^{2+}-independent phospholipase A_2 (type VIA)
ITO	indium tin oxide
LC-MS	liquid chromatography coupled with mass spectrometry
LDL	low-density lipoprotein
LDLr($^{-/-}$)	low-density lipoprotein receptor (deficient)
LPA	lysophosphatidic acid
LPAAT	lysophosphatidic acid acyltransferase
LPAP	lysophosphatidic acid phosphatase
LPA$_x$	lysophosphatidic acid receptor
LPC	lysophosphatidylcholine
LPL	lipoprotein lipase
LPP	lipid phosphate phosphatase
LPS	lipopolysaccharide
LRP-1	low density lipoprotein receptor-related protein 1
LysoPLD	lysophospholipase D
MAG(K)	monoacylglycerol (kinase)

MALDI	matrix-assisted laser desorption/ionization
MAPK	mitogen-activated protein kinase
MARCO	macrophage receptor with collagenous structure
MCP-1	monocyte chemoattractant protein-1
M-CSF	macrophage colony stimulating factor
ME-SIMS	matrix-enhanced secondary ion mass spectrometry
MGAT	monoacylglycerophosphate acyltransferase
MHC	major histocompatibility complex
mmLDL	minimally modified low-density lipoprotein
MMP	matrix metalloproteinase
MOMA-2	monocyte/macrophage antibody-2
moxLDL	mildly oxidized low-density lipoprotein
MRM	multiple reaction monitoring mode
MTP	microsomal triglyceride transfer protein
m/z	mass-to-charge ratio
nd	not determined
NEFA	non-esterified fatty acid
NFAT	nuclear factor of activated T cells
NK	natural killer
NM-MHC	non-muscle myosin heavy chain
NO	nitric oxide
Npc1l1	Niemann-Pick C1-like 1
NS	non significant
OD	optical density
oxLDL	oxidized low-density lipoprotein
oxPAPC	1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphocholine
PA	phosphatidic acid
PAS	periodic acid-Schiff
PBS	phosphate buffered saline
PC	phosphatidylcholine
(RT-)PCR	(real-time) polymerase chain reaction
PDGF	platelet-derived growth factor
PG	prostaglandin
PLA	phospholipase A
PLD	phospholipase D
PMC	peritoneal mast cell
p-mφ	peritoneal macrophage
PPAR	peroxisome proliferator-activated receptor
PPRE	PPAR responsive elements
PS	phosphatidylserine
PSGL-1	P-selectin glycoprotein ligand-1
PTCA	percutaneous transluminal coronary angioplasty
PTEN	phosphatase and tensin homologue deleted on chromosome 10

(m)RNA	(messenger) ribonucleic acid
ROS	reactive oxygen species
Scd1	stearoyl-coenzyme A desaturase 1
SEM	standard error of the mean
Sgpl1$^{(-/-)}$	S1P lyase (deficient)
SIMS	secondary ion mass spectrometry
SMC	smooth muscle cell
S1P	sphingosine 1-phosphate
$S1P_x$	sphingosine 1-phosphate receptor
SphK	sphingosine kinase
sPLA	secretory phospholipase A
SPP	S1P phosphatase
SRBI	scavenger receptor class B, member 1
SREBP-1	sterol regulatory element binding transcription factor
TCR	T cell receptor
TF	tissue factor
TGF-β	transforming growth factor-β
Th	T helper cell
THI	2-acetyl-4-tetrahydroxybutylimidazole
TIA	transient ischemic attack
TIC	total ion current
TLR	Toll-like receptor
TNF-α	tumor necrosis factor-α
TNF-R	tumor necrosis factor receptor
TOF-SIMS	time-of-flight secondary ion mass spectrometry
Treg	regulatory T cell
V	volt
VCAM-1	vascular adhesion molecule-1
VLA-4	very late antigen-4
VLDL	very low-density lipoprotein
VSMC	vascular smooth muscle cell
v/v	volume/volume

List of Publications

Full Papers

Bot M, McAleese L, Bot I, Van Berkel TJC, Heeren RMA, Biessen EAL. Lipid Cartography of Mouse Atherosclerotic Plaques by Cluster-TOF-SIMS Imaging. *Manuscript in preparation.*

Bot M, Bot I, De Jager SCA, Van Berkel TJC, Biessen EAL. Lysophosphatidic Acid Destabilizes Atherosclerotic Plaques in ApoE$^{-/-}$ Mice Partly by Activating Perivascular Mast Cells. *Manuscript in preparation.*

Bot M, Bot I, De Jager SCA, Van Berkel TJC, Biessen EAL. LPA Administration Changes Atherosclerotic Plaque Phenotype in ApoE$^{-/-}$ Mice by Affecting Vascular Smooth Muscle Cell Content. *Manuscript in preparation.*

Bot M, Bot I, Westra M, De Jager SCA, Van Santbrink PJ, Van der Hoeven G, Gijbels MJ, Müller-Tidow C, Varga G, Van Berkel TJC, Van Veldhoven PP, Nofer JR, Biessen EAL. Hematopoietic Absence of Sphingosine 1-Phosphate Lyase Decreases Atherosclerotic Lesion Development in LDL Receptor Deficient Mice. *Submitted.*

Bot M, Bot I, Lopez-Vales R, Saulnier-Blache JS, Van De Lest CHA, Helms JB, David S, Van Berkel TJC, Biessen EAL. Atherosclerotic Lesion Progression Changes Lysophosphatidic Acid Homeostasis to Favor Its Accumulation. *Submitted.*

Bot M, Nofer JR, Van Berkel T, Biessen EA. Lysophospholipids: Two-Faced Mediators in Atherosclerosis. Future Lipidol. *Future Lipidology* 2007;2:341-356.

Nofer JR*, Bot M*, Brodde M, Taylor PJ, Salm P, Brinkmann V, van Berkel T, Assmann G, Biessen EA. FTY720, a Synthetic Sphingosine 1-Phosphate Analogue, Inhibits Development of Atherosclerosis in Low-density Lipoprotein Receptor Deficient Mice. *Circulation.* 2007;115:501-508. *authors contributed equally

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Bot M, Bot I, Westra MM, De Jager SCA, Van Santbrink PJ, Gijbels MJ, Van Berkel TJC, Van Veldhoven PP, Nofer JR, Biessen EAL. Hematopoietic Absence of Sphingosine 1-Phosphate Lyase Decreases Atherosclerotic Lesion Development in LDL Receptor Deficient Mice. (oral presentation at the AHA Scientific Sessions 2008) *Circulation.* 2008,118:II.

Baitsch D, Telgman R, Varga G, Müller-Tidow C, Bot M, Nofer JR. Apolipoprotein E (ApoE) Induces an Anti-Inflammatory Phenotype in Macrophages. (poster presentation at the AHA Scientific Sessions 2008) *Circulation.* 2008;118:II.

Curriculum Vitae

Martine Bot werd op 5 november 1979 geboren te Dordrecht. In 1998 behaalde zij haar VWO diploma aan het Johan de Witt-gymnasium te Dordrecht. In afwachting van selectierondes voor een opleiding in de burgerluchtvaart heeft zij een jaar administratieve werkzaamheden verricht bij Autobedrijven van Wijngaarden te Papendrecht. In 1999 begon zij met de studie Biomedische Wetenschappen aan de Universiteit Leiden, waar zij in 2000 *cum laude* het propaedeutisch examen behaalde. Tijdens de doctoraalfase van de studie vond er een overgang plaats naar het Bachelor-Master systeem en in 2002 behaalde zij *cum laude* haar Bachelor in de Biomedische Wetenschappen van de Universiteit Leiden. Op basis van haar studieresultaten werd ze toegelaten tot het excellente studenten traject van de faculteit Geneeskunde. Tijdens haar Master in de Biomedische Wetenschappen combineerde zij dit traject met haar stage bij de vakgroep Medische Pharmacologie van het Leiden/Amsterdam Center for Drug Research onder leiding van Dr. M.R. Kruk en Prof. Dr. E.R. de Kloet. Door deze combinatie konden twee korte buitenlandse stages in het Instituut voor Experimentele Geneeskunde van de Hongaarse Academie voor Wetenschap in Boedapest gerealiseerd worden. Hierna deed zij als student een onderzoeksstage bij de vakgroep Biofarmacie van het Leiden/Amsterdam Center for Drug Research onder leiding van Prof. Dr. E.A.L. Biessen en Prof. Dr. Th.J.C. van Berkel. In 2004 studeerde zij aan de Universiteit Leiden *cum laude* af in de Biomedische Wetenschappen op het onderzoek getiteld “Effects of reducing thrombogenic lipids on atheroma: prevention of thrombotic events after plaque rupture”. Voor dit onderzoek ontving zij de S.E. de Jongh award voor beste project op het gebied van medicijn onderzoek.

Van september 2004 tot oktober 2008 verrichte zij promotieonderzoek bij de afdeling Biofarmacie van het Leiden/Amsterdam Center for Drug Research aan de Universiteit Leiden. Onder leiding van Prof. Dr. E.A.L. Biessen en Prof. Dr. Th. J.C. van Berkel werd onderzoek uitgevoerd naar de rol van 2 specifieke vetten, lysofosfatidaat en sfingosine 1-fosfaat, in de ontwikkeling van atherosclerose, dat in dit proefschrift beschreven staat. In 2007 ontving zij een fellowship van de Dutch Atherosclerosis Society voor de beste presentatie met de titel “FTY720, a Synthetic Sphingosine 1-Phosphate Analogue, Inhibits Development of Atherosclerosis in LDLr$^{-/-}$ Mice”.

Sinds oktober 2008 is zij aangesteld als post-doctoraal onderzoeker bij de afdeling Biofarmacie van het Leiden/Amsterdam Center for Drug Research.