University of Groningen

Modulation of the inflammatory response in hibernation and calorie restriction

Reitsema, Vera Annemarie

DOI:
[10.33612/diss.194860187](https://doi.org/10.33612/diss.194860187)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):
Reitsema, V. A. (2021). *Modulation of the inflammatory response in hibernation and calorie restriction: lessons for sepsis from metabolic extremes*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen. <https://doi.org/10.33612/diss.194860187>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

**Modulation of the inflammatory response in
hibernation and calorie restriction**

Lessons for sepsis from metabolic extremes

Vera Annemarie Reitsema

This MD/PhD-project and the publication of this thesis were financially supported by Foundation the Cock-Hadders, the University Medical Centre Groningen, the University of Groningen and the Graduate School GUIDE at the University of Groningen.

Provided by thesis specialist Ridderprint, ridderprint.nl

Printing: Ridderprint

Layout and design: Erwin Timmerman, persoonlijkproefschrift.nl

Cover concept by Vera Reitsema

Graphical summaries were created with biorender.com

©Copyright V.A. Reitsema, Groningen, The Netherlands, 2021

All rights reserved. No parts of this thesis may be reproduced, stored in a retrieval system or transmitted in any form or by any means without prior permission of the author.

university of
 groningen

Modulation of the inflammatory response in hibernation and calorie restriction

Lessons for sepsis from metabolic extremes

PhD thesis

to obtain the degree of PhD at the
University of Groningen
on the authority of the
Rector Magnificus Prof. C. Wijmenga
and in accordance with
the decision by the College of Deans.

This thesis will be defended in public on

Thursday 23 December 2021 at 14.30 hours

by

Vera Annemarie Reitsema

born on 25 February 1991
in The Hague

Supervisor

Prof. R.H. Henning

Co-supervisor

Dr. H.R. Bouma

Assessment Committee

Prof. F.J. van Spronsen

Prof. R.A. Hut

Prof. L. Koenderman

TABLE OF CONTENTS

	List of abbreviations	6
Chapter 1.	Introduction	9
Chapter 2.	Metabolic resuscitation strategies to prevent organ dysfunction in sepsis	19
Chapter 3.	Dietary restriction augments endogenous hydrogen sulfide in neutrophils boosting their functionality in murine sepsis	65
Chapter 4.	Calorie restriction increases vulnerability of progeroid <i>Ercc1^{Δ/-}</i> mice to (neuro)inflammation	93
Chapter 5.	Hibernation metabolism detailed by integrated metabolomics and proteomics analysis of Syrian hamster liver	115
Chapter 6.	Phase specific suppression of neutrophil function in hibernating Syrian hamster	147
Chapter 7.	Summary & General discussion	163
Appendices	Nederlandse samenvatting	197
	Acknowledgements	201
	About the author	203
	List of publications	205

LIST OF ABBREVIATIONS

3-MST	3-mercaptopyruvate sulfurtransferase	GAD	glutamic acid decarboxylase
5'-AMP	5'-adenosine monophosphate	GCN2	general control nonderepressible 2
AAT	aspartate/cysteine aminotransferase	G-CSF	granulocyte colony-stimulating factor
ADP	adenosine diphosphate	GM-CSF	granulocyte-macrophage colony stimulating factor
AE	arousal early	GPX4	glutathione peroxidase 4
AKI	acute kidney injury	GSH	glutathion
AL	arousal late	GSR	glutathionreductase
AMP	adenosine monophosphate	GSSG	glutathione disulfide
AMPK	AMP-activated protein kinase	GST	glutathione-S-transferase
Ang	angiopoietin	H₂S	hydrogen sulfide
ATP	adenosine triphosphate	HDAC	histone/protein deacetylase
BHMT	betaine-homocysteine methyltransferase	HIF-1α	hypoxia-inducible factor-1 α
BTLA	B and T lymphocyte attenuator	HMGB1	high mobility group box 1
CBS	cystathionine β -synthase	HO-1	heme oxygenase-1
CCL	C-C chemokine ligands	HPA axis	hypothalamo-pituitary-adrenocortical axis
CCR2	C-C chemokine receptor type 2	ICAM	intercellular adhesion molecule
CDO	cysteine oxygenase	ICU	intensive care unit
CGD	chronic granulomatous disease	IDH	isocitrate dehydrogenase
CLP	cecal ligation and puncture	IFN	interferon
CO	carbon monoxide	IGF-1	insulin growth factor-1
CR	calorie restriction	LAD	leukocyte adhesion deficiency
CRP	C-reactive protein	LBP	LPS binding protein
CS	citric synthase	LPS	lipopolysacharide
CSE	cystathionine- γ -lyase	Mac-1	macrophage-1 antigen
CSO	cysteine sulfinate decarboxylase	MAT	methionine adenosyltransferase
CXCR2	C-X-C motif chemokine receptor 2	MDA	malondialdehyde
DAMPs	damage-associated molecular patterns	MDH	malate dehydrogenase
DEM	differentially expressed metabolite	Mfn2	mitofusin 2
DEP	differentially expressed protein	MODS	multi-organ dysfunction
DLD	dihydrolipoyl dehydrogenase	MPO	myeloperoxidase
DLST	dihydrolipoyl succinyltransferase	MPTPs	mitochondrial permeability transition pores
DR	dietary restriction	MS	methionine synthase
Drp1	dynammin related protein	mTOR	mechanistic target of rapamycin
eIF2α	eukaryotic initiation factor 2	NAC	N-acetylcysteine
EOF	every other day fasting	NAD⁺/NADH	nicotinamide adenine dinucleotide, oxidized versus reduced respectively
ETC	electron transport chain	NADPH	nicotinamide adenine dinucleotide phosphate
G6PD	glucose-6-phosphate dehydrogenase		
GABA	gamma-aminobutyric acid		

NaHS	sodium sulfide	TCA cycle	citric acid cycle, also known as tricarboxylic acid cycle
NDUF	NADH:ubiquinone oxidoreductase supernumerary subunit	TL	torpor late
NETs	neutrophil extracellular traps	TLR	toll-like receptor
NF	normal fed	UCP1	uncoupling protein 1
Ngal	neutrophil gelatinase-associated lipocalin	WE	winter euthermia
NO	nitric oxide	γ-GCS	gamma-glutamylcysteine synthetase
NOS	nitric oxide synthase	$\Delta\Psi_m$	mitochondrial membrane potential
Nrf2	nuclear factor erythroid 2-related factor 2		
OGDC	oxoglutarate dehydrogenase complex		
OGDH	oxoglutarate dehydrogenase		
OPA1	optic atrophy 1		
PAG	DL-propargylglycine		
PCT	procalcitonin		
PD-1	programmed cell death protein 1		
PDC	pyruvate dehydrogenase complex		
PKD	pyruvate dehydrokinase		
PGE2	prostaglandin E2		
PLP	pyridoxal 5'-phosphate		
PRR	pattern recognition receptor		
ROS	reactive oxygen species		
RRT	renal replacement therapy		
S1P	sphingosine-1-phosphate		
SADH	succinic semialdehyde		
SCS	succinyl-CoA synthetase		
SDH	succinate dehydrogenase		
SE	summer euthermia		
Sirt-1	sirtuin-1		
SOD	superoxide dismutase		
SOFA score	sequential (sepsis-related) organ failure assessment score		
sRAGE	soluble receptor for advanced glycation end- products		
SSADH	succinic semialdehyde dehydrogenase		
sTREM1	soluble triggering receptor expressed on myeloid cells 1		
suPAR	soluble urokinase-type plasminogen activator receptor