

Discovery and characterization of new glucosylated metabolites: pathophysiological consequences Meijer, H.N.J.

Citation

Meijer, H. N. J. (2023, November 2). *Discovery and characterization of new glucosylated metabolites: pathophysiological consequences*. Retrieved from https://hdl.handle.net/1887/3655909

Version:	Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/3655909

Note: To cite this publication please use the final published version (if applicable).

Discovery and characterization of new glucosylated metabolites:

pathophysiological consequences

H.N.J. Meijer

ISBN/EAN: 978-94-6473-256-6

Cover: Design and layout: dr. D. Augustijn

Copyright © 2023. H.N.J. Meijer

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

Discovery and characterization of new glucosylated metabolites: pathophysiological consequences

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Leiden, op gezag van de rector magnificus prof. dr. ir. H. Bijl, volgens besluit van het college voor promoties te verdedigen op donderdag 2 november 2023 klokke 11.15 uur door Hubrina Neeltje Jacomina Meijer geboren te Goes in 1990

Promotor:

Prof. dr. J.M.F.G. Aerts

Co-promotor:

dr. R.G. Boot

Promotiecommissie:

Prof. dr. H.S. Overkleeft Prof. dr. M. van der Stelt Prof. dr. R.T. Dame Prof. dr. T. Hankemeier Prof. dr. C.J.M. de Vries, Universiteit van Amsterdam Prof. dr. R.H.L. Houtkoper, AMC – Universiteit van Amsterdam

"Develop a passion for learning. If you do, you will never cease to grow."

Anthony J. D'Angelo

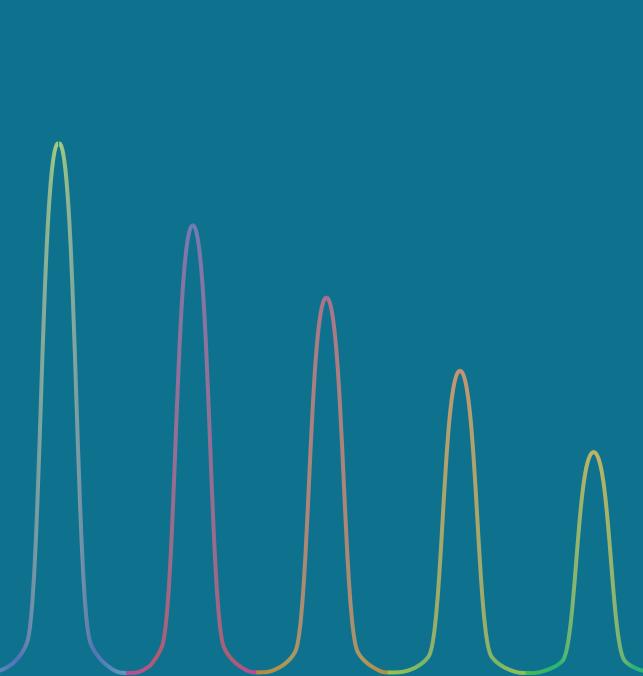


Table of Contents

Chapter 1 - Introduction and outline	13
Lysosomes and lysosomal diseases	14
GBA: catalytic features	19
GBA2 and GBA3	22
Physiological relevance of transglycosylation	23
Acceptors in transglucosylation	23
Goals of the thesis	26
Other published contributions to the research field	27
References	28

Chapter 2 - Mass spectrometric quqntification of glycosylated metabolites of cholesterol analoques using (isotope) standards	35
Abstract	37
Introduction	38
Results	40
Quantification of Glc7DHC, GlcD ₃ and GlcDesm by LC-MS/MS	40
Mass spectrometric analysis, fragmentation and elution spectrum	41
Intra/Inter assay variation	43
Carryover	45
Storage of samples	45
Impurities	49
Detection of glycosylated sterols in biological samples	49
Discussion	52
Experimental procedures	53
Materials	53
Methods	54
Supplementary information	60
References	62

Chapter 3 - Formation and degradation of glucosyl-desmosterol	
Abstract	67
Introduction	68
Results	71
In vitro formation and degradation of GlcDesm by transglucosylation by β-glucosidases	71
Measurement of GlcChol and GlcDesm in GD spleen	75
Discussion	76
Acknowledgements	77
Supplementary information	78
Experimental procedures	79
Materials	79
Methods	79
References	81
Chapter 4 - Formation, degradation and natural occurrence of Glucosyl- 7-dehydrocholesterol and Glucosylated vitamin D ₃	87
Abstract	89
Introduction	90
Results	93
In vitro formation and degradation of Glc7DHC by transglucosylation by β-glucosidases	93
Conversion of Glc7DHC into GlcD ₃	97
In vitro formation and degradation of GlcD ₃ by transglucosylation by β -glucosidases	97
Measurement of GlcChol, Glc7DHC and GlcD ₃ in GD spleen	100
Measurement of GlcChol, Glc7DHC and GlcD ₃ in skin	101
Discussion	102
Supplementary information	104
Experimental procedures	106
Materials	106
Methods	107
References	110

Chapter 5 - Potential role of GBA3 in formation and degradation of glycosylated metabolites	
Abstract	119
Introduction	120
Results	121
Formation and degradation of glucosylated metabolites by GBA3	121
Discussion	123
Acknowledgements	123
Experimental procedures	125
Materials	125
Methods	125
References	127

Chapter 6 - General discussion and perspectives for future research	
General discussion	
Perspectives for future research	
New metabolites to be explored	133
Glucosylated metabolites: the missing link?	135
Potential acceptor abnormality that might promote causing glucosylated metabolites abnormalities	137
Untargeted discovery of glycosylated metabolites	138
Formation and occurrence of Xylosylated metabolites	140
Conclusion	141
References	142
Summary	150
Samenvatting	153
About the author - Curriculum Vitae	156
List of publications	158

Addendum	
Addendum I: Glucosylated cholesterol in mammalian cells and tissues: formation and degradation by multiple cellular β-glucosidases	159
Addendum II: Human glucocerebrosidase mediates formation of xylosyl-cholesterol by β -xylosidase and transxylosidase reactions	160

Acknowledgement