

Inconspicuous offender

Citation for published version (APA):

Bitorina, A. (2020). *Inconspicuous offender: pathophysiological role of oxidized-low density lipoprotein in metabolic disease*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20200929ab>

Document status and date:

Published: 01/01/2020

DOI:

[10.26481/dis.20200929ab](https://doi.org/10.26481/dis.20200929ab)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

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Appendices

Summary

The main focus of this thesis was to elucidate the role of oxidized lipids with a primary focus on oxLDL in the pathophysiology of metabolic diseases such as NASH, NPC1 and cancer. A variety of *in vitro*, *in vivo* and clinical study methods were employed to assess the disease progression markers affected by oxLDL or derivatives thereof such as inflammation, metabolism and response to treatment. In addition, we also sought to validate the use of antibodies against oxLDL as a promising readily-available therapeutic tool to prevent the detrimental effects of oxLDL in cancer.

Chapter 1 provides a global overview of lipids, in particular oxidized lipids, lysosomal enzymes such as cathepsin D and the role they play in metabolic diseases

Chapter 2 explores the direct effects of oxLDL on the inflammatory status of macrophages, which are thought to be the main drivers of inflammation in diseases featuring dyslipidemia, as well as verifying the ability of anti-oxLDL antibodies to prevent these effects. Here OxLDL was found to contribute to lysosomal lipid-induced hepatic inflammation and increasing anti-oxLDL IgM autoantibodies ameliorates oxLDL induced inflammation *in vitro*.

Chapter 3 evaluates the effects of CTSD inhibition on the oxLDL mediated modulation of inflammation in macrophages in order to explore its therapeutic viability. The findings demonstrated that inhibition of the proteolytic function of the lysosomal enzyme CTSD reduced inflammation in oxLDL-loaded BMDMs.

Chapter 4 covers a novel attribute of an oxidized lipid (27-hydroxycholesterol) with promising lipid lowering therapeutic potential that shows different effects in men versus women. Here it was observed that cholesterol derivative 27HC affects inflammation differently in males versus females. These differences between males and females are thought to be due to inherent differential expression patterns of the estrogen receptor subtypes between the two sexes.

Chapter 5 Reveals the current state of our general understanding of the effects of oxLDL in cancer

Chapter 6 aimed to further elucidate the metabolic effects of oxLDL in cancer. Here it was found that oxLDL caused a metabolic shift towards glycolysis, stabilized HIF1- α under normoxic conditions and induced autophagy in pancreatic cancer cell line KLM-1. In addition, anti-oxLDL antibodies prevented the oxLDL mediated activation of HIF1- α and autophagy.

Chapter 7 showcases preliminary results of an ongoing *in vivo* experiment which looked into the effects of pneumococcal immunization in a NASH-HCC mice model. Here it was uncovered that anti-oxLDL immunization using heat-inactivated pneumococci reduces tumor burden and growth rate in murine NASH-derived HCC.

Appendices

Finally, **chapter 8** discusses the overall conclusions of this thesis and addresses open questions that can be further investigated in future research in this context.