Virus-host metabolic interactions: using metabolomics to probe oxidative stress, inflammation and systemic immunity

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Publication of this thesis was financially supported by:

Shimadzu Benelux

The Herman J Coster foundation

ISBN: 978-90-9030097-9

Cover design: Since 1961 graphic design

Printed by**:** Print Service Ede

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Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,
volgens besluit van het college voor Promoties
te verdedigen op dinsdag 20 december 2016
klokke 11:15 uur.

door

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geboren te Klerksdorp, Zuid Afrika
in 1987

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This research is supported by the Netherlands Organisation for Scientific Research (NWO)-ZonMW grant number 435002027, and the Virgo consortium, funded by the Dutch government project number FES0908.

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Preface

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Some of the earliest documentation on the interaction between humans and viruses were depicted in Egyptian paintings almost 3000 years ago (*1580-1350 BC)*. The artwork depicted a man with deformed lower extremities and it is believed that he suffered from poliomyelitis. In 1789 Dr Michael Underwood documented and provided the first clinical description of poliomyelitis which he called "debility of the lower extremities". In the late 19th century it was the work of Louis Pasteur and Charles Chamberland that laid the groundwork for the field of virology as we know it today. The development of filters gained widespread popularity as a new scientific technique, especially after the 1884 paper entitled 'A filter permitting to obtain physiologically pure water' published by Charles Chamberland [1], as the use of filters permitted the removal of bacteria thought to be the main pathogenic agent at the time. Pasteur used filters during his work on rabies in the 1880s and was able to get a bacteria-free, watery extract which was able to cause symptoms of disease upon exposure. Pasteur was also able to make the conceptual leap that the pathogenic agent could be a 'micro-organism infinitesimally small' [2]. The word virus of Latin origin was later used as description for this poisonous fluid originally referred to as "contagium vivum fluidum". It was only in 1908 that the Austrian physicians Karl Landsteiner and Erwin Popper hypothesized that poliomyelitis may be caused by a virus. Since then the field of virology has become a burgeoning field. Even today still the global population faces unprecedented challenges from viruses, old and new, evident in the 2014 Ebola epidemic in West Africa as well as the more recent 2016 Zika virus in South America.

Viruses are completely dependent on the host machinery for replication and survival, and their ability to hijack cellular pathways and machinery can effectively turn host cells into virus producing factories [3]. The virus-host interactions have been extensively studied in the field of immunology, molecular biology, transcriptomics and proteomics. Immunology is used to elucidate host-virus interaction relating to the effector functions of the innate and adaptive immune responses. Transcriptomics and proteomics are used to investigate viral induced changes and hijacked pathways, as well as host defence systems against infection. More recently however an appreciation has been garnered for the role of the host metabolites and metabolism during infection, as well as their ability in shaping an immunological response. The use of metabolomics, a continuously developing field, has enabled us to measure the highly dynamic host metabolism as well as the perturbations induced during viral infections. Applications of metabolomics in the field of virology range from fundamental work of biological insight to more ground-breaking work in identifying biomarkers used for disease diagnosis, prediction of severity, prognosis and even biomarkers that are able to predict outcome of therapeutic intervention.

In this thesis, metabolomics is used to study the role of the host-virus interaction on a metabolic level. A special emphasis is directed on the role of inflammation and oxidative stress on the metabolic level, as part of the innate immune response against viral infection. We chose respiratory syncytial virus (RSV) and hepatitis B virus (HBV) as candidate viruses to metabolically study their role in acute respiratory infection and chronic hepatitis B infection. Secondly we also investigated infant metabolic and immunological consequences of *in utero* exposure to antiretroviral intervention and human immunodeficiency virus (HIV). Collectively,

established targeted metabolomics approaches in conjunction with newly developed metabolomics methodologies and complemented with other "omics" techniques, were used to address pertinent questions related to host metabolic functioning and alterations during viral infection. *In vitro* RSV studies together with *in vivo* patient based studies relating to chronic HBV infection and *in utero* exposure too antiretroviral and HIV were used to address these questions. The thesis is divided into three research parts containing: i. the analytical methodology development work, ii. *in vitro* based metabolomics and iii. patient based metabolomics.

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