Interventions to increase apolipoprotein A-I transcription in HepG2 cells

Valorisation

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Atherosclerosis, a chronic inflammatory disease of the artery wall, is the main underlying pathology in cardiovascular disease (CVD) development and is initiated by a disturbed lipid and lipoprotein profile (dyslipidemia). Despite remarkable improvements in therapy and prevention, CVDs still remain the leading cause of mortality worldwide [1]. On a yearly basis, CVDs account for more than 17.3 million deaths and expectations are that this number will grow to more than 23.6 million within the year 2030 [2]. In the United States (U.S.), about 85.6 million people are currently living with some form of CVD or with CVD-related after-effects. Clearly, this goes hand in hand with high CVD-related health costs. In fact, from 2011 to 2012 the direct CVD-related costs in the U.S, which reflect e.g. hospital services, prescribed medications and home health care, were estimated on 193.1 billion dollars. Other CVD-related indirect costs, such as the loss of future productivity, were estimated to be about 123.5 billion dollars. Together this adds up to 316.6 billion dollars in one year [3]. In attempt to reduce the CVD related mortality and the related healthcare costs, extensive research on ways to decrease CVD risk factors is needed. In order to develop interventions that could reduce CVD risk, it is essential to increase our knowledge on underlying pathways that lead to atherosclerosis. Furthermore, research is needed to create new possibilities to target prevention or treatment programs for this pathology.

It is well accepted that increased Low Density Lipoprotein cholesterol (LDL-C) is a major risk for CVD development. This is why therapies aiming to reduce LDL-C have already been successfully developed. However, after effective LDL-C lowering treatment, there often remains a residual risk for CVD development. Clearly, there is a need to discover additional therapies to further reduce the risk for CVD development. Nowadays, there is a wealth of evidence from *in vitro* and *in vivo* studies using pharmaceuticals to increase the production of apolipoprotein A-I (apoA-I). Increasing apoA-I, the main protein of High Density Lipoprotein (HDL) particles, is a promising strategy to protect against CVD development [4]. For example, the intravenous infusion of recombinant apoA-I Milano reduced atheroma size in humans [5] and using apoA-I mimetics [6,7], cholesterol efflux capacity is clearly increased. By increasing cholesterol efflux capacity from macrophages in the vessel wall to HDL particles, cholesterol can be transported back to the liver, where it can be used for the production of amongst others bile acids. Moreover, recent evidence suggests that increased cholesterol-efflux capacity protects against development of CVD [8,9] and recurrence of CVD [10].
While there already are some natural products available on the market that decrease the “atherogenic” LDL-C concentrations, such as margarines containing plant sterols or plant stanols, natural dietary products that aim to increase functional HDL particles, in order to increase reverse cholesterol transport and cholesterol-efflux capacity, are not available yet. Development of functional foods that increase functional HDL particle production could help consumers that are looking for a solution to maintain a healthy lipid and lipoprotein profile. Natural BET inhibitors could eventually also be used as a functional food product to reduce the risk for development of other types of diseases, as BET family members are involved in many biological processes. ApoA-I increaser JQ1(+), for example, is also used as a male anti-fertility in mice [11], because it inhibits testes specific

BRDT. In addition, BET inhibitors possess anti-inflammatory effects [12] and are involved in the suppression of proto-oncogenes [13]. The finding that BET inhibition is beneficial for treatment of many types of disease highlights the importance of research related to this topic.

Societal and economic relevance

From a scientific point of view, the research described in this dissertation contributed to the fundamental understanding of metabolic disturbed processes and regulatory factors involved in apoA-I transcription and ways to target apoA-I transcription by natural means. After performing safety assessments, the natural compounds that were discovered using both the PPARα screening (**chapter 4**) and the in silico screening (**chapter 7**), could be tested in human studies. Moreover, our research provides leads for future *in vivo* studies, not only within the field of BRD4 inhibition, but also within the field of functional food production. If the discovered natural compounds appear to be safe to use in human subjects, and if they appear to be effective in increasing apoA-I and thereby in inducing cholesterol efflux capacity, this will be of high societal and economic relevance.

Valorisation is described by the National Valorisation Commission as “the process of creating value from knowledge by making knowledge suitable and/or available for societal and/or economic use, and by translating that knowledge into competitive products, services, processes and commercial activities”. As discussed earlier, the costs for treatment of CVD related diseases could decline when an additional therapy to increase functional HDL or apoA-I production is available.
The future production of functional food products is a nice example of the translation of obtained knowledge into practice, and from an economical perspective, the production of functional foods contributes to development of the food industry. The Dutch Technology Foundation STW, which is part of the Netherlands Organization for Scientific Research (NWO), and which is partly funded by the Ministry of Economic Affairs, supported the research that was presented in this dissertation. Within this STW project there is close collaboration between scientific researchers, industry and the government. Where researchers contribute to the development of fundamental knowledge, the collaboration with these partners could facilitate a translation of the obtained results into commercially available products.

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