Intestinal cholesterol absorption in humans

Impact

This dissertation focused on associations between genetic variants with cholesterol metabolism, in particular with intestinal cholesterol absorption. It was shown that different single nucleotide polymorphisms (SNPs) were associated with intestinal cholesterol absorption. These SNPs were located in or close to the following genes: ABCG5, *ABCG8, EIF2B5, EPHB3, C4orf26, CDKL2, NR3C2, LOC285626, BMP6, HLA-G, HLA-H, WBSCR27, WBSCR28, TMTC4, and COL4A2.* Moreover, to better understand the complex network of intestinal cholesterol absorption, an intestinal cholesterol absorption network was built. Furthermore, in an intervention study, the effects of a non-nutrient that lowers intestinal cholesterol absorption on gene expression profiles were investigated. It was found that gene expression profiles of high-cholesterol and low-cholesterol absorbers were distinct after the intake of plant stanol esters. Altogether, results have contributed to a better understanding of the complex intestinal cholesterol network. In the following paragraphs, the potential impact of the main findings in terms of societal, economic, and scientific relevance will be addressed. Finally, possible implications for the translation of the findings into practice will be discussed.

Societal and economic relevance

Despite the significant advancement over the past decades in its prevention and treatment, cardiovascular disease (CVD) continues to be the primary cause of morbidity and mortality globally (1). Moreover, its burden on the EU economy is substantial and - according to estimations of the European Heart Network - imposes annually an economic burden of over €200 billion (2). A well-known risk marker for the development of CVD is the concentration of cholesterol in the blood. Many processes play a role in cholesterol homeostasis, including intestinal cholesterol absorption. It is widely recognized that the amount of cholesterol absorbed by the small intestine differs between individuals due to various factors, including genetic background (3). In fact, individuals can be categorized as high-cholesterol or low-cholesterol absorbers, and individuals with a high cholesterol absorption rate may exhibit a more favorable response to interventions aimed at reducing intestinal cholesterol uptake compared to those with a low cholesterol absorption rate (4). Importantly, the rate of

cholesterol absorption has been associated with different metabolic diseases (5). Therefore, it is important to understand in more detail 1) the mechanism of intestinal cholesterol absorption and 2) associations between genetic variants related to the amount of cholesterol absorbed.

Translation into practice

Currently, there is a high demand for tools and methods that can support and enhance the interpretation of the physiological and metabolic effects of carrying genetic variants, particularly SNPs. These SNPs are common genetic variations found in the human genome and are crucial for the emerging field of precision nutrition and medicine. As the business activity surrounding genetic testing rapidly grows, numerous companies are providing genetic tests for various purposes, surpassing the traditional roles of healthcare professionals. Therefore, the need for robust tools and methods to analyze and understand the biological implications of genetic variants under a non-business influence is of utmost importance.

Healthcare professionals can benefit from a better understanding of the mechanism of intestinal cholesterol absorption and the relationship between genetic variants with intestinal cholesterol absorption. With the knowledge that high levels of LDL-C have limited life quality and increase the chance to develop different metabolic diseases, the practical need to understand this variation is crucial. This dissertation now provides evidence that genetic variation affects intestinal cholesterol absorption. However, it is unclear if these SNPs also link to the efficacy of LDL lowering interventions. If not, it is even possible that the characteristic of having a high cholesterol absorption is a risk factor independent of (changes in) serum LDL cholesterol concentrations. To date, however, there is no (genetic) test that differentiates high-cholesterol absorbers from those of low-cholesterol absorbers. Finding a tool that can distinguish these two groups from each other may help in the future healthcare professionals to optimize the treatment for individuals using precision nutrition and medicine. Since genetic tests like SNPs are more robust and easier to interpret as compared to analyzing serum non-cholesterol sterols, this may be a more suitable strategy. Therefore, a validated SNP or set of SNPs that can be linked to these characteristics is a promising tool for future precision nutrition approaches.

Scientific relevance

Other researchers can build upon the scientific conclusions of this dissertation which provides a foundation for further research. However, it is crucial to critically evaluate and validate the results before drawing any definitive conclusions. Therefore, further experimental studies are needed to determine the functional effects of the identified genes and genetic variants on intestinal cholesterol absorption and on other pathways affected. For instance, to investigate the effect of particular genetic variants on cholesterol absorption, CaCo-2 cells cultured on a transwell system can be used as it serves as a model for intestinal epithelial cells. These cells can be transfected with genes of interest and used in a cholesterol absorption assay. Also, studies are needed the establish relationships between (a set of) genetic variants with SNPs LDL-C responses. Also, the causal connection between cholesterol absorption and various metabolic disease warrants further study. Our findings may ultimately contribute to improve the management of elevated blood cholesterol concentrations.

In conclusion, the research presented in this thesis has made a valuable contribution to the scientific community. The findings have undergone or are undergoing the process of publication in peer-reviewed scientific journals. Findings have also been presented at scientific meetings. As a result, the knowledge obtained is readily available to scientists, facilitating further investigations into the mechanism of intestinal cholesterol absorption and the influence of genetic variation on cholesterol absorption levels.

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