A computational framework to analyse heterogeneous plasma lipoprotein metabolism

Sips - CMSB - Poster Flash

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Fianne Sips, Christian Tiemann, Peter Hilbers, Natal van Riel

Department of Biomedical Engineering, Eindhoven University of Technology, the Netherlands

Introduction
The size and lipid content distributions of plasma lipoproteins co-determine metabolic and cardiovascular disease risks. Understanding of the mechanisms which control lipoprotein metabolism therefore has high clinical relevance. While much of the physiology of lipoprotein metabolism is known, the interplay of the mechanisms leading to increased cardiovascular risk is not fully understood.
To aid further quantitative understanding of the mechanisms underlying phenotype changes in mouse models a novel computational model of plasma lipoprotein metabolism in mice was developed. The model was successfully applied to wild-type mouse phenotypes as well as to altered phenotypes resulting from common genetic deficiency models and data sets in which the effects of an intervention were observed in time.
Methods
The computational model entails detailed descriptions of heterogeneous lipoproteins, coupled with a phenomenological kinetic model describing lipoprotein metabolism. Both HDL and VLDL metabolism and a framework of compositional calculations based on multiple data sets of C57Bl/6J mice were incorporated in the model. The model was developed and parameterised to describe the cholesterol and triglyceride profiles [1] obtained from fast protein liquid chromatography (FPLC) separation.
Results
The novel computational model was able to reproduce experimentally observed plasma lipoprotein profiles of wild-type mice. Model simulations of the steady state profiles provided predictions of the unobserved underlying lipid and lipoprotein distributions and fluxes.
By applying parameter perturbations qualitative predictions of the lipoprotein profile of common genetically modified mouse models were successfully made. The model therefore described not only wild-type metabolism, but also protein deficiency models such as the SR-B1 or PLTP knock-out models. The model was also applied to FPLC profiles obtained following an intervention entailing LXR activation by TO901317.
Conclusion
A novel computational framework is presented which is able to describe the metabolism and FPLC profiles of wild type mice. The model provides opportunities to investigate a variety of complex phenotypes in which lipoprotein metabolism is disturbed resulting in changes in particle composition and size.

References
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