Genes affecting triglyceride metabolism: from steatosis to lipodystrophy
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Summary
In Chapter 1, intra- as well extracellular triglyceride metabolism is described at the molecular level. The role of lipases and apolipoproteins as well as transcriptional factors regulating these genes is illustrated.

In Chapter 2, we discuss the gene expression in atherosclerosis. This chronic process in the arterial wall is usually confined to specific sites where the blood flow is more turbulent and the shear stress is low. We focus on the role of each of three major cell types (i.e. endothelial cells, smooth muscle cells and monocyte/macrophages), in the arterial wall and their gene expression profile in healthy and atherosclerotic condition. Special attention is given to the vascular role of nuclear transcription factors, such as peroxisome proliferator-activated receptor gamma (PPAR\(_\gamma\)) that is mainly known for its involvement in triglyceride storage in adipocytes.

In chapter 3, a novel gene family that is expressed in the endothelial cells of human aorta is described. The apolipoprotein L gene cluster is located at chromosome 22q31 and consists of 4 homologous genes. We show that this gene cluster has emerged recently in the evolution as the result of tandem gene duplication. ApoL3 is shown to most probably represent the ancestral gene, with ApoL2 as closest relative at the DNA level. Interestingly, amino-acid sequences diverge more than DNA sequences, hinting at a fast functional divergent evolution. Most significantly, ApoL1 contains a signal peptide and is therefore secreted into plasma and is associated with HDL-particles. Presumably, apoL4 has lost its function during the evolution and has become a pseudogene because of the lack of gene expression in examined tissues.

Chapter 4 describes the function of apoL2 and apoL3. The divergent intracellular localization of these two proteins, ER for ApoL2 versus Golgi for ApoL3, is illustrated by specific antibodies as well as by Green fluorescent protein (GFP) fusion proteins. Although, these two genes are highly homologous, we found that they have opposite effects on intracellular triglyceride levels in the different cell types studied. ApoL2 over-expression increases intracellular triglyceride levels and apoL3 decreases it. Both genes are also expressed in cells specialized in triglyceride storage such as macrophages and adipocytes. In vivo, over-expression of apoL2 induced steatosis in mice livers, whereas apoL3 reduced the level of steatosis.

Chapter 5 describes a novel gene, Lipase H (LIPH) that is homologous to triglyceride lipase family. LIPH is localized on human chromosome 3q27–q28 and it was mainly expressed in intestine, lung, and pancreas. Lipase H is a secreted protein with an apparent molecular weight of 63 kDa. Although its structure resembles that of other triglyceride lipases, its substrate was not identified. Like other members of this gene family, LIPH may be involved in lipid and energy metabolism, but its precise function is yet to be determined.

Chapter 6 describes a patient with a mutation in the PPAR\(_\gamma\) gene. This nuclear transcription factor is involved in adipocyte differentiation and triglyceride storage. Activating this gene
by specific drugs has been widely used in the clinic for treating diabetic patients. Although this particular subject was not obese, she had all the characteristic features of metabolic syndrome such as diabetes with extreme insulin resistance, dyslipidemia and hypertension due to mutation in the DNA binding domain of PPARγ. We show that this specific mutation indeed disrupts PPARγ function, leading to PPARγ haplo-insufficiency.

Chapter 7 describes all types of lipodystrophy and the associated metabolic abnormalities in affected patients. The generalized lipodystrophies are often diagnosed by pediatricians because of their striking appearance, whereas partial lipodystrophies become apparent during adult life. Therefore, these patients are often not recognized and are treated as metabolic syndrome patients. We emphasize the importance of recognizing the patients with lipodystrophy due to genetic abnormalities, because of the therapeutic consequences.

Finally Chapter 8 summarizes the findings in this thesis and the role of genes involved in triglyceride metabolism. Fat storage in adipose tissue as well as in non-adipose tissue is discussed. Special attention has been given to the significance of communication between fundamental researchers and clinicians to improve our understanding of the pathophysiology of diseases to be able to define new therapeutic targets and design new drugs. Therefore, bidirectional transfer of information, i.e from bench to bedside as well as from bedside to bench is of utmost importance.