

Nuclear transcription factors: new opportunities for lipid lowering

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Hypoalphalipoproteinaemia is the most common lipoprotein abnormality. Reduced plasma concentrations of HDL-cholesterol and apolipoprotein A-I, the major HDL apolipoprotein, have been found to be major independent risk factors for coronary artery disease. Plasma HDL concentrations are determined by the interaction of environmental and genetic factors, but the major genetic factors are ill-defined. Our laboratory has been studying the transcriptional control of HDL metabolism, and we have focused on the role of specific transcription factors of the nuclear hormone receptor gene superfamily therein. Nuclear receptors are ligand-activated transcription factors which after activation bind to regulatory regions in target genes, thereby modulating their expression level. As such they integrate signals coming from the environment, allowing the organism to adapt by changing the expression of specific target genes. We have identified the nuclear receptors peroxisome proliferator-activated receptor α (PPAR α), retinoic acid receptor-related orphan receptor α (ROR α) and Rev-erb α as transcriptional regulators of HDL metabolism. These receptors act by influencing the transcription of genes determining HDL levels, such as apolipoproteins A-I and A-II. In addition, absence of their expression profoundly

perturbs HDL metabolism. In *staggerer* mutant mice absence of ROR α expression leads to a profound hypoalphalipoproteinaemia and an increased susceptibility for atherosclerosis, due to a decreased transcription of the apolipoprotein A-I gene in the intestine. PPAR α , another key-player in the response of HDL to hypolipidaemic fibrates and dietary factors, regulates both apolipoprotein A-I and A-II gene expression. Through genetic studies we have now identified a PPAR α variant in human subjects which may act as a dominant negative form. We speculate that individuals expressing high levels of this variant may be resistant to fibrates. Furthermore, we have determined the human PPAR α gene structure and identified several polymorphisms which are associated with altered serum lipid and apolipoprotein A-I levels in type 2 diabetic patients. Altogether, these results identify nuclear receptors, such as PPAR α , involved in the control of HDL metabolism. Since these genes code for ligand-activated receptors, further research will be aimed at identifying pharmaceutical compounds which may prove of value in the treatment of hypoalphalipoproteinaemia and other disorders of lipid and lipoprotein metabolism. The references provide a selected reading list.

Nuclear transcription factors: HDL metabolism: Peroxisome proliferator-activated receptor α

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Abbreviations: PPAR α , peroxisome proliferator-activated receptor α ; ROR α , retinoic acid receptor-related orphan receptor α .

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