STUDIES ON TWO PROTEINS WITH POTENTIAL IMPLICATIONS FOR ATHEROSCLEROSIS – LIPOLYTIC ENZYME CARBOXYL ESTER LIPASE AND NADPH OXIDASE SUBUNIT NOX4

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Abstract

Atherosclerosis is a progressive disease that is characterised by accumulation of lipid deposits in the subendothelial layer of arteries and subsequent inflammatory responses in the lesion regions. One of the primary risk factors associated with atherosclerosis is an atherogenic serum lipid profile with elevated levels of low-density lipoprotein (LDL) cholesterol. Central processes in the development of atherosclerotic lesions are the retention and oxidation of lipoproteins in the vascular wall. In vascular disease states such as atherosclerosis, the production of reactive oxygen species (ROS) in the artery wall is increased such that the antioxidant defence systems are overwhelmed which leads to "oxidative stress", a hallmark of virtually all vascular pathophysiological states.

The work presented in this thesis includes studies on two proteins with potential implications for processes involved in cardiovascular disease. The first protein, carboxyl ester lipase (CEL), is an enzyme that acts in concert with other lipolytic enzymes in the intestine to ensure adequate uptake of dietary lipids, but it is also found in the circulation where it may interact with plasma cholesterol. We found that a polymorphic repeat region in the CEL gene was associated with serum lipid phenotype in such a way that individuals with alleles containing a shorter repeated region had lower total and LDL cholesterol levels. The repeats have potential functional implications for secretion and protein stability of CEL, therefore our results supports the notion that CEL may be involved in determining the plasma lipid profile.

In our studies aimed at elucidating the origin and role of circulating CEL we showed that CEL was present in human atherosclerotic lesions and that it was expressed and secreted by monocytes and macrophages. However, CEL was also present in LDL-containing fractions from serum donors, which suggests an alternative route by which CEL can become accumulated in the lesion regions. Analysis of the transcriptional regulation of CEL in macrophages revealed that CEL expression in these cells depends on the binding of upstream stimulatory factor(s) (USF) 1 and/or 2 and at least one yet unknown factor to the promoter.

The second protein, Nox4, has been implicated as a catalytic subunit of the superoxide-producing enzyme NADPH-oxidase. In this study, the role of Nox4 in vascular smooth muscle cells (VSMCs) was investigated. By specifically targeting the Nox4 mRNA in cultured mouse VSMCs with antisense oligonucleotides, the NADPH-dependent superoxide production was markedly attenuated. Based on the results of this study, we suggest that Nox4 is involved in the superoxide generating system that is operating in these cells.

Key words: Carboxyl ester lipase, repeat, polymorphism, atherosclerosis, macrophage, upstream stimulatory factor, NADPH oxidase, superoxide, antisense, Nox4

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