

FATTY ACIDS INDUCE POTENTIALLY ATHEROGENIC CHANGES IN EXTRACELLULAR MATRIX PROTEOGLYCANs

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ABSTRACT

Insulin resistance and type 2 diabetes (T2D) are associated with an increased prevalence of atherosclerotic cardiovascular disease (CVD). A key step in the initiation of atherogenesis is retention of low density lipoproteins (LDL) in the intima by chondroitin sulfate (CS)-rich proteoglycans (PG). In addition, heparan sulfate (HS)-containing PGs in liver have a major physiological function in the retention and internalization of chylomicron and very low density lipoprotein (VLDL) remnant particles. Elevated levels of circulating non-esterified fatty acids (NEFA) are part of the dyslipidemia of insulin resistance and T2D. The objective of this thesis was to investigate the impact of chronic NEFA elevation on extracellular matrix (ECM) PGs and its implications for diabetes-associated CVD.

Linoleate incubation decreased the PG secretion and gene expression of the core proteins of versican, and to a lesser extent, syndecan-1, in the human liver-derived cell line HepG2. The GAG chains of secreted PGs had a lower CS content. PGs extracted from livers of the insulin-resistant hyperlipidemic Zucker *fa/fa* rat carried GAG chains with increased CS content at the expense of HS compared with livers from their lean littermates. These changes resulted in a reduced capacity to bind β -VLDL remnant particles. Incubation of primary cultures of human arterial smooth muscle cells with linoleate or palmitate increased the gene expression of the core proteins of versican, biglycan, perlecan and decorin; and of CS synthase, CS-6 and CS-4 sulfotransferases, key enzymes for the polymerization and sulfation of chondroitin chains. These effects were accompanied by increased PG secretion. Secreted PGs were enriched in chondroitin/dermatan sulfate and with a higher extent of sulfation, resulting in a more efficient binding of LDL compared with PGs from control cells. Investigation of the signaling pathways involved in the linoleate-induced increase of versican expression showed that it was mediated by an extracellular signal-regulated kinase (ERK)-dependent activation of the transcription factor CCAAT-enhancer binding protein (C/EBP) β . These findings suggest a novel role for C/EBP β in the fatty acid-induced changes of ECM.

Chronic NEFA elevation resulted in changes in the properties of matrix PGs that may contribute to generate a remnant-rich dyslipidemia and to precondition the arterial intima for lipoprotein deposition. Therefore, normalization of the fatty acid homeostasis should be considered a key target in the treatment of the atherogenic dyslipidemia of insulin resistance.

KEYWORDS: proteoglycans, glycosaminoglycans, fatty acids, smooth muscle cells, hepatocytes, LDL binding, remnant clearance, insulin resistance, type 2 diabetes

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