



Title	Up-regulation of aldose reductase activity in cultured mesangial cells overexpressing human aldose reductase gene is associated with increased TGF-beta1 and collagen IV expression
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EM-11 Effect of the microsomal triglyceride transfer protein -493 G/T polymorphism and type 2 diabetes mellitus on LDL subfractions

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Introduction. Genetic variation in the microsomal triglyceride transfer protein (MTP) affects the secretion pattern and plasma concentration of apolipoprotein (apoB)-containing lipoproteins and the common functional -493 G/T polymorphism has been reported to influence plasma lipids levels. Recent data suggest that carriers of the T allele might be more sensitive to detrimental factor such as features of the insulin resistance syndrome. Since type 2 diabetes is associated with obesity and insulin resistance, the present study investigated the effect of this polymorphism on plasma lipids, apoB and LDL subfractions in 281 Chinese type 2 diabetic patients and 364 non-diabetic controls.

Methods. The polymorphism for each subject was determined by polymerase chain reaction, restriction enzymatic action and subsequent electrophoresis on 3% metaphor agarose gel.

Results. The frequency of the rare T allele was 0.162 and 0.126 in subjects with and without diabetes respectively. Diabetic subjects had significant higher body mass index and waist hip ratio than the controls ($p < 0.01$). There were no differences in the effect of the polymorphism on plasma lipids and apoB in the 2 groups. However, the TT genotype was associated with a higher concentration of small dense LDL-III than the GT or GG variants in the diabetic subjects ($p = 0.01$) whereas no such effect was observed in the controls. In the diabetic patients, age, plasma triglyceride and the MTP genotype were independent determinants of LDL-III concentrations in linear regression analysis ($R^2 = 10\%$, $p < 0.05$) whereas in the controls, only plasma triglyceride and age were important determinants ($R^2 = 15\%$, $p < 0.01$).

Conclusion. The -493 G/T polymorphism has a minor effect on LDL subfraction pattern in Chinese and the effect is only apparent in the presence of type 2 diabetes.

EM-12 Up-regulation of aldose reductase activity in cultured mesangial cells overexpressing human aldose reductase gene is associated with increased TGF-beta1 and collagen IV expression

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Introduction: Increased flux of glucose through the polyol pathway involving the enzyme aldose reductase (AR) has been implicated in the pathogenesis of diabetic nephropathy. However, the proposed mechanisms to explain the role of AR and its interaction with other pathogenetic pathways, such as enhanced production of advanced glycation endproducts (AGEs), TGF-beta1 and extracellular matrix including collagen IV in diabetic nephropathy remain controversial. In the present study, we examined the effect of increased AR activity on TGF-beta1 and collagen IV expression in mesangial cells derived from transgenic mice expressing human AR (hAR) with AGEs-BSA application.

Methods: We established a transgenic mouse model expressing hAR in kidney mesangial cells. Primary cultures of the mesangial cells from hAR transgenic (TG) and wildtype (WT) mice were treated with 0.1mg/ml of either AGEs-BSA or non-glycated BSA for 24 hours with and without the addition of an AR inhibitor, zopolrestat (0.01mM). hAR mRNA and protein expression were measured by RT-PCR and Western blotting respectively. AR activity, and mRNA levels of TGF-beta1 and collagen IV in mesangial cells were examined by spectrophotometry and RT-PCR.

Results: hAR mRNA and protein expression were demonstrated in TG, but not in WT mesangial cells. AR activity was also increased in TG mesangial cells ($P < 0.05$ versus WT mesangial cells). Enhanced AR activity was seen in both WT and TG mesangial cells ($P < 0.05$), when treated with AGEs-BSA. The increase in AR activity in the presence of AGEs-BSA was accompanied by increases in TGF-beta1 and collagen IV transcripts in mesangial cells, which reached statistical significance only in the cells from TG animals ($p < 0.01$). Preliminary data show that this increased TGF-beta1 mRNA expression and AR activity can be partly abolished by the addition of an AR inhibitor.

Conclusion: These results suggest that AR may be involved in the increased expression of TGF-beta1 which contributes to the mesangial cell proliferation and matrix protein production observed in diabetic nephropathy, in part through an interaction with AGEs.

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