

OXIDISED LOW DENSITY LIPOPROTEIN DECREASES HIT-T15 PANCREATIC BETA CELLS VIABILITY VIA DECREASE IN ANTIOXIDANT ACTIVITIES

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ABSTRACT

Increased serum levels of oxidised low density lipoprotein (oxLDL) as found in patients with Type 2 diabetes, can induce severe oxidative stress in exposed cells which then can lead to cell death. Our study aimed to determine how the decreased cells antioxidant status of pancreatic beta cells induced by oxLDL affects their viability. We used various concentrations of CuCl₂ oxidised LDL to determine its cytotoxic effect as well as the influence on the antioxidant enzymes activity in HIT-T15 pancreatic beta cells. A significant cellular formation of reactive oxygen species (ROS) was detected within 3 hours incubation of HIT-T15 pancreatic beta cells with 1.5 mg/mL of oxLDL. The formation of ROS was accompanied by a simultaneously loss of cellular glutathione. However, a significant reduction in cell viability was only measured after 10 hours incubation with oxLDL. The enzymatic activities of catalase and peroxidase remained unchanged for 24 hours. These results suggest that loss of glutathione induced by oxLDL is not sufficient to cause HIT-T15 cell death as they can be still protected from cytotoxic effects of oxLDL by the other antioxidant defenses such as catalase and peroxidase.

Key words: Oxidised low density lipoprotein, reactive oxygen species, glutathione, catalase, peroxidase

INTRODUCTION

The progressive dysfunction and destruction of pancreatic beta-cells are hallmarks of the onset and progression of type 2 diabetes mellitus (T2DM) (Plaisance *et al.*, 2016). Chronic excess of cholesterol and metabolic fuels (such as glucose and non-esterified palmitate) together with genetic factors are among the common causes that elicit beta-cell damage over time (Favre *et al.*, 2011). High levels of oxLDL are strongly correlated with obesity-associated metabolic syndrome (Holvoet *et al.*, 2004) and/or the development of T2DM (Nakhjavani *et al.*, 2010). Several studies have shown that low plasma levels of high density lipoprotein (HDL) together with increased levels of oxLDL are strongly linked to T2DM (Cubedo *et al.*, 2015; Rohrer *et al.*, 2004). Oxidative stress caused by oxLDL was 23% higher in obese and 56% higher in T2DM patients (Marin *et al.*, 2015). Additionally, specific antibodies against oxLDL were found in

patients with T2DM while oxLDL receptors were found in both human and rodent islet beta-pancreatic cells (Bellomo *et al.*, 1995; Vavuli *et al.*, 2016).

A previous study showed that exposure of pancreatic beta cell lines to oxLDL leads to reduced gene expression with subsequent reduced insulin protein production and therefore insulin secretion (Ceriello, 2000). Kaneto *et al.* (2010) found that oxLDL activates mitogen-activated protein kinase (MAPK) 8 (also known as c-Jun amino terminal kinase, JNK) which is one of the hallmarks of oxidative stress. Activation of JNK signaling by oxLDL leads to decrease in the PDX-1 DNA binding activity to the insulin promoter which causes reduction of insulin gene transcription. This event leads to impaired insulin expression and consequently pancreatic beta cell dysfunction. OxLDL also induces the inducible cyclic AMP repressor (ICER) that silences the expression of genes containing cAMP response elements (CRE) and ultimately causes defect in cell insulin genes expression (Favre *et al.*, 2011). These cumulative evidences further strengthen the association of

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