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TCTAP A-138

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BACKGROUND The prevalence of atherosclerotic cardiovascular disease is higher in patients with type 2 diabetes, a disorder characterized by hyperinsulinemia and insulin resistance. The role of hyperinsulinemia as an independent participant in the atherogenic process has been controversial. Therefore, we examined whether insulin could regulate the expression of scavenger receptors responsible for oxidized low-density lipoprotein (oxLDL) uptake in DCs, a critical step in atherogenesis. In addition, we investigated the impact of insulin on DC maturation regarding changes in phenotype and cytokine secretion.

METHODS Immature DCs were cultured with different concentrations of insulin (1nmol/L, 10nmol/L, 100nmol/L) in the absence or presence of LY294002 or wartmannin for 24 hours. The expression of the scavenger receptors SR-A and CD36 was determined by real-time PCR and western blot analysis. Furthermore, DCs were incubated with Dil-labelled oxLDL. The Dil-oxLDL-incorporated fraction was investigated by flow cytometry analysis. Finally, flow cytometry analysis was used to investigate immunophenotypic protein expression (CD83 and CD11a). DC-differentiation was evaluated using the expression of BDCTCTAP A-1/-2 by flow cytometry analysis. Supernatant cytokine measurements were used for immune function assays.

RESULTS The incubation of DCs with insulin enhanced, in a dose-dependent manner, the gene and protein expression of SR-A and CD36. This effect was partially abolished by wartmannin, a phosphatidylinositol-3-OH kinase (PI3 kinase) inhibitor. But LY294002 did not inhibit the effect of insulin on scavenger receptors' expression. High concentration of insulin increased the oxLDL-uptake capacity of DCs. Blockage of the scavenger receptors SR-A and CD36 significantly reduced oxLDL uptake. Furthermore, high concentration of insulin induced DC-maturation and triggered differentiation of DCs in myeloid and plasmacytoid DCs. Finally, high concentration of insulin decreased IL-10 secretion and increased IL-6release.

CONCLUSION This study suggests that hyperinsulinemia could promote DC activation and oxLDL uptake and thus may contribute to atherogenesis in patients with type 2 diabetes.