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Crosstalk between fatty liver and pancreatic adiopocytes accentuates local inflammation and impairs insulin secretion

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Obesity-linked ectopic fat accumulation increases the risk of the development of type-2 diabetes mellitus. While liver steatosis (NAFLD) is well accepted as an adverse factor, pancreatic fat accumulation is controversially discussed. This study aims to characterize the pancreatic fat compartment and its role in islet function.

The immuno histological analysis of human pancreatic resections suggests that differentiated adipocytes, identified by oil red and adiponectin staining, infiltrated the exocrine tissue and occasionally even the endocrine tissue. Islets surrounded by adipocytes displayed normal architecture and endocrine cell distribution as determined by insulin, glucagon and somatostatin immunostaining. The proximity of adipocytes to islets correlated with an increased number of CD68-positive cells within the islets.

In order to examine pancreatic fat cells in more detail primary preadipocytes were isolated and differentiated *in vitro* to adipocytes. Both, preadipocytes and adipocytes, were exposed to palmitate and fetuin-A to mimic a cross-talk between fatty pancreas and fatty liver. Under control culture condition, cytokine production was low. The exogenously addition of palmitate and fetuin-A to the culture medium stimulated IL6, CXCL8 and CCL2 expression and secretion of primary pancreatic preadipocytes as well as of differentiated adipocytes. This stimulation was TLR4 dependent. When the effect of pancreatic fat cell on islet function was examined in a co-culture system, cytokine production of preadipocytes was further increased.

In addition, in isolated human islets from organ donors, fetuin-A and palmitate increased IL-1β, IL6 and CXCL8 mRNA levels. The up-regulation of IL-1β occurred exclusively in macrophages which infiltrated the islets. As expected, palmitate stimulated apoptotic islet cell death, whereas Fetuin-A did not alter beta-cell death. Fetuin-Areduced glucose-induced insulin secretion (GIIS). The effect of fetuin-A was abrogated by an inhibitor (SP600125) of the stress kinase JNK. Fetuin-A inhibition of GIIS was also counteracted by an increase of extracellular Ca2+, but, interestingly, persisted in the presence of TLR4 inhibition.

These results suggest that in obese humans increased plasma levels of palmitate, i.e. long chain saturated fatty acids, and fetuin-A, released from fatty liver, stimulate cytokine production of pancreatic fat cells which augments local inflammation. An additional fetuin-A-mediated metabolic crosstalk of fatty liver with islets directly affects GIIS.