Review

MOLECULAR METABOLISM

What role do fat cells play in pancreatic tissue?

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ABSTRACT

Background: It is now generally accepted that obesity is a major risk factor for type 2 diabetes mellitus (T2DM). Hepatic steatosis in particular, as well as visceral and ectopic fat accumulation within tissues, is associated with the development of the disease. We recently presented the first study on isolated human pancreatic adipocytes and their interaction with islets [Gerst, F., Wagner, R., Kaiser, G., Panse, M., Heni, M., Machann, J., et al., 2017. Metabolic crosstalk between fatty pancreas and fatty liver: effects on local inflammation and insulin secretion. Diabetologia 60(11):2240—2251.]. The results indicate that the function of adipocytes depends on the overall metabolic status in humans which, in turn, differentially affects islet hormone release.

Scope of Review: This review summarizes former and recent studies on factors derived from adipocytes and their effects on insulin-secreting β-cells, with particular emphasis on the human pancreas. The adipocyte secretome is discussed with a special focus on its influence on insulin secretion, β-cell survival and apoptotic β-cell death.

Major Conclusions: Human pancreatic adipocytes store lipids and release adipokines, metabolites, and pro-inflammatory molecules in response to the overall metabolic, humoral, and neuronal status. The differentially regulated adipocyte secretome impacts on endocrine function, i.e., insulin secretion, β-cell survival and death which interferes with glycemic control. This review attempts to explain why the extent of pancreatic steatosis is associated with reduced insulin secretion in some studies but not in others.

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Keywords Fatty pancreas; Adipocytes; Paracrine signalling; Insulin secretion; β-cell mass; Type 2 diabetes mellitus (T2DM)

1. INTRODUCTION

One major risk factor for the development of type 2 diabetes mellitus (T2DM) is obesity [2,3]. Obesity comprises not only increased subcutaneous fat deposition but also visceral fat accumulation [4]. Ectopic fat deposits include adipocyte infiltration into the parenchyma as well as fat droplet formation within tissue cells other than adipocytes. In the liver, hepatocytes accumulate fat in intracellular lipid droplets, whereas, in the pancreas, lipids are mainly stored in adipocytes which infiltrate the parenchyma [5,6]. Pancreatic adipocyte infiltration was first described in 1933 [7]. In humans, pancreatic steatosis can be detected *in vivo* using a variety of non-invasive techniques, including CT and MRI [8,9]. The link between pancreatic fat and glycemic control is still a matter of some debate [8—11]. While studies on cohorts comprising non-diabetic and diabetic humans do not report an association between the degree of pancreatic fat content and insulin secretion, an analysis of humans with impaired glucose tolerance and/or increased fasting glucose suggests that glycemic control deteriorates as the amount of pancreatic fat increases. Human studies addressing the cause and consequence of pancreatic adipocyte infiltration were comprehensively reviewed recently [12,13]. Ectopic fat storage is caused not only by adipocyte infiltration but also occurs within exocrine parenchyma and islet cells [14,15]. The degree of intracellular triglyceride storage in lipid droplets, however, does not correlate with cellular dysfunction or cell death, albeit circulating or locally released free fatty acids may affect cellular functions [10,16]. Here, we focus on putative paracrine effects of pancreatic adipocytes on islet function rather than on the reason why fat cells accumulate within the pancreas. Further questions are whether the secreted factors, the so-called "secretomes" of preadipocytes and adipocytes, depend on the (ectopic) location of the fat cells i.e., whether they are organ-dependent, and whether humoral factors characteristic for the diabetogenic milieu have an impact on the secretome. Finally, we address whether fat cell infiltration has a bearing on proper islet function.

1.1. The fat cell: a storage cell with a large secretome

The white adipocyte stores lipids in large central droplets. Upon stimulation, e.g., sympathetic activation during starving conditions, adipocytes secrete metabolites such as fatty acids, glycerol, and lysophospholipids. They control lipid metabolism and secrete lipoprotein lipase (LPL), cholesteryl ester transfer protein (CETP), apolipoprotein E (ApoE), retinol-binding protein-4 (RBP-4), and neutrophil gelatinase-associated lipocalin (NGAL). In addition, adipocytes act as endocrine cells by secreting adipokines [17]. Adipokines are defined here as adipocyte-specific proteins with hormone-like

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Received February 22, 2019 • Revision received April 10, 2019 • Accepted May 1, 2019 • Available online 7 May 2019

https://doi.org/10.1016/j.molmet.2019.05.001

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activity. The hormones leptin and adiponectin regulate food intake, satiety, and hunger. Additional hormones produced by adipocytes are apelin, resistin, visfatin, omentin, and angiopoietin-like 4 (ANGPTL-4). Fat cells also promote cell growth and vascularization by the secretion of insulin-like growth factor (IGF-1), fibroblast growth factor (FGF-1, FGF-2), transforming growth factors (TGF-α, TGF-β), nerve growth factor (NGF), macrophage colony-stimulating factor (M-CSF), heparin-binding epidermal growth factor (HB-EGF), vascular endothelial growth factor (VEGF), and hepatocyte growth factor (HGF). Last, but not least, they produce chemokines and cytokines including interleukins (IL-6, IL-8, IL-10, IL-15, IL-18), macrophage migration inhibitory factor (MIF), monocyte chemoattractant protein (MCP-1), macrophage inflammatory protein (MIP-1α), and stromal cell-derived factor (SDF-1), thereby contributing to local low grade inflammation. A variety of complementary factors and acute phase reactants, plasminogen activator inhibitor (PAI-1), C-reactive protein (CRP), haptoglobin (Hp), pentraxin-related protein (PTX3), and serum amyloid A (SAA) can be added to the list of the adipocyte secretome (see also Figure 1). As a consequence, fat cells have many diverse humoral and local paracrine effects on organ function and the whole body's metabolic status. Whether adipocytes exert beneficial or adverse effects depends on the metabolic environment. Our studies on adipocytes isolated from different origins, i.e., subcutaneous, perivascular, visceral, and renal sinus, suggest that the secretomes differ between the compartments [18–20]. However, a systematic assessment of differences between pancreatic adipocytes and adipocytes from other tissues is not yet available.

Adipocytes originate from precursor cells, the preadipocytes. Between 15 and 50% of fat cells in adipose tissue are estimated to be preadipocytes [21,22]. While they secrete cytokines and growth factors, preadipocytes neither store lipids nor do they produce adiponectin. This hormone, therefore, is a marker for differentiated adipocytes. Consequently, the different secretomes of preadipocytes and adipocytes may exert distinct paracrine effects, such as, and in our case, on islet function. Table 1 summarizes the mRNA levels of secreted substances from human pancreatic preadipocytes and adipocytes cultured under standard conditions. Interestingly, upon differentiation adipocytes synthesize large amounts of adiponectin mRNA while leptin mRNA levels were higher in preadipocytes than in adipocytes. The data further indicate that T2DM may affect the differentiation of preadipocytes into adipocytes.

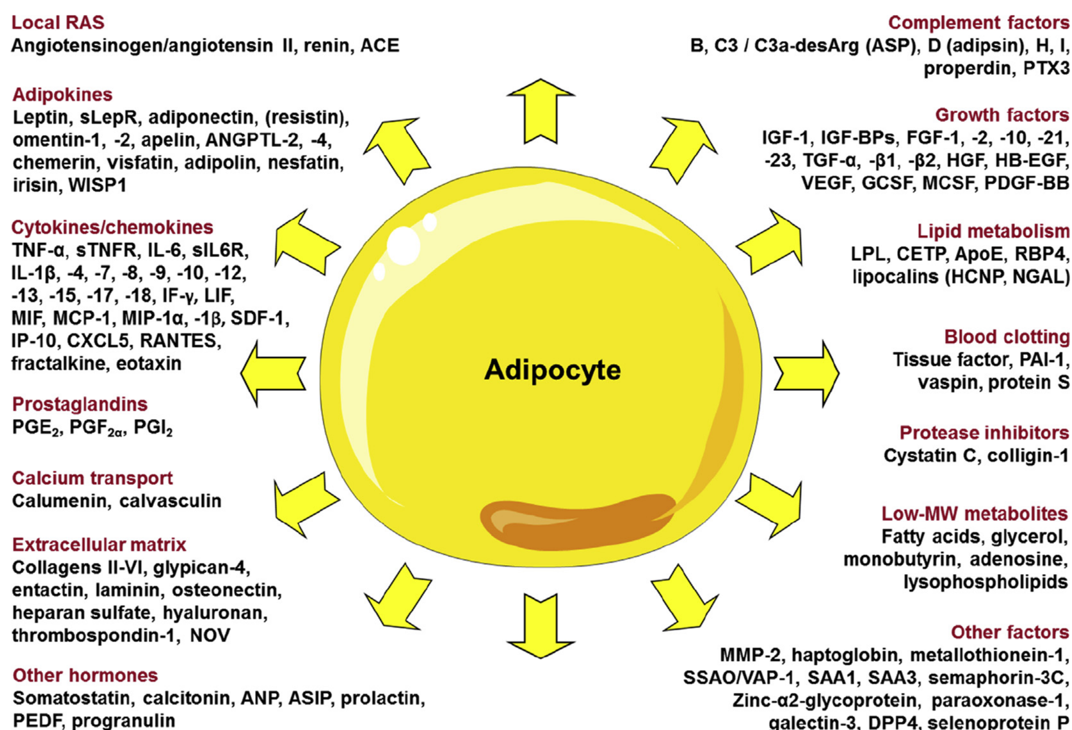

Figure 1: Overview of the white adipocyte's secretory activity. Updated and modified version of Figure 1 in [Staiger H, Häring HU. White adipose tissue's humoral mediators of chronic subclinical inflammation. Int. J. Adipose Tissue 1 (2007): 17–23]. Resistin is produced by murine adipocytes only. Abbreviations: ACE – angiotensin-converting enzyme; ANGPTL – angiopoietin-like protein; ANP – atrial natriuretic peptide; Apo – apolipoprotein; ASIP – agouti signaling protein; ASP – acylation-stimulating protein; CETP – cholesteryl ester transfer protein; CXCL – C-X-C motif chemokine; DPP – dipeptidyl peptidase; FGF – fibroblast growth factor; GCSF – granulocyte-colony-stimulating factor; HB-EGF – heparin-binding epidermal growth factor; HCNP – hippocampal cholinergic neurostimulating peptide; HGF – hepatocyte growth factor; IF – interferon; IGF – insulin-like growth factor; IGF-BP – IGF-binding protein; IL – interleukin; IP – IF-γ-induced protein; LIF – leukemia inhibitory factor; LPL – lipoprotein lipase; MCP – monocyte chemoattractant protein; MCSF – macrophage-colony-stimulating factor; MIF – macrophage migration inhibitory factor; MIP – macrophage inflammatory protein; MMP – matrix metalloproteinase; MW – molecular weight; NGAL – neutrophil gelatinase-associated lipocalin; NOV – nephroblastoma overexpressed protein; PAI – plasminogen activator inhibitor; PDGF – platelet-derived growth factor; PEDF – pigment-epithelium-derived factor; PG – prostaglandin; PTX – pentraxin-related protein; RANTES – regulated on activation, normal T cell expressed and secreted protein; RAS – renin-angiotensin system; RBP – retinol-binding protein; SA – serum amyloid; SDF – stromal-cell-derived factor; sIL6R – soluble IL6 receptor; sLepR – soluble leptin receptor; sTNFR – soluble TNF receptor; SSAO – semicarbazide-sensitive amine oxidase; TGF – transforming growth factor; TNF – tumor necrosis factor; VAP – vascular adhesion protein; VEGF – vascular endothelial growth factor; WISP – WNT1-inducible-signaling pathway protein.

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Table 1 — The comparison of mRNA levels of substances secreted by human pancreatic preadipocytes and adipocytes cultured and differentiated *in vitro*; ND, non-diabetic; PD, prediabetic; D, diabetic. Given are the mRNA levels as read counts (rlog) ± SEM ($n = 4$).

Secretome	Preadipocytes			Adipocytes		
	ND	PD	D	ND	PD	D
Adipokines						
Adiponectin	3.73 ± 0.03	3.83 ± 0.04	3.78 ± 0.02	**10.38 ± 0.61**[a]	**8.44 ± 1.04**[a]	**6.84 ± 1.11**[a]
Leptin	10.15 ± 0.24	9.31 ± 0.71	10.69 ± 0.56	**5.84 ± 0.24**[a]	**6.06 ± 0.27**[a]	**7.00 ± 0.44**[a]
Apelin	9.32 ± 0.22	8.68 ± 0.41	8.9 ± 0.48	**7.8 ± 0.23**[a]	**7.73 ± 0.10**[a]	8.23 ± 0.31
ANGPTL-2	10.8 ± 0.13	10.81 ± 0.27	10.7 ± 0.17	11.47 ± 0.23	10.82 ± 0.18	11.07 ± 0.12
ANGPTL-4	11.48 ± 0.21	11.64 ± 0.28	11.31 ± 0.11	11.06 ± 0.2	**10.51 ± 0.34**[a]	10.69 ± 0.16
Visfatin	9.56 ± 0.11	9.53 ± 0.05	9.89 ± 0.31	9.55 ± 0.17	9.2 ± 0.14	9.2 ± 0.25
Adipolin[b]	5.33 ± 0.06	5.4 ± 0.10	5.3 ± 0.12	5.21 ± 0.11	4.93 ± 0.12	5.15 ± 0.12
Nesfatin	10.98 ± 0.10	10.99 ± 0.10	10.9 ± 0.23	11.24 ± 0.20	11.37 ± 0.14	11.34 ± 0.19
Irisin	6.5 ± 0.36	6.38 ± 0.26	6.1 ± 0.45	**8.16 ± 0.34**[a]	**7.43 ± 0.38**[a]	**7.86 ± 0.28**[a]
WISP1	8.62 ± 0.42	8.91 ± 0.39	8.69 ± 0.51	8.29 ± 0.50	9.41 ± 0.35	9.22 ± 0.32
LepR	9.33 ± 0.24	10.13 ± 0.30	9.98 ± 0.23	**8.17 ± 0.32**[a]	**8.41 ± 0.29**[a]	**8.24 ± 0.27**[a]
Cytokines						
IL-6	10.91 ± 0.08	10.75 ± 0.44	10.91 ± 0.11	**8.00 ± 0.27**[a]	**8.57 ± 0.05**[a]	**8.21 ± 0.38**[a]
MCP-1	8.67 ± 0.34	8.70 ± 0.11	7.94 ± 0.25	8.49 ± 0.37	7.88 ± 0.09	7.23 ± 0.28
IL-8[b]	4.19 ± 0.23	4.40 ± 0.07	3.85 ± 0.14	3.53 ± 0.29	**3.21 ± 0.12**[a]	3.28 ± 0.16
LIF[b]	6.58 ± 0.16	7.07 ± 0.30	6.55 ± 0.11	6.14 ± 0.08	**6.13 ± 0.16**[a]	6.00 ± 0.12
CXCL5[b]	2.95 ± 0.11	3.06 ± 0.04	2.80 ± 0.11	**3.50 ± 0.13**[a]	3.38 ± 0.14	**3.41 ± 0.04**[a]
Growth factors						
IGF-1[b]	5.96 ± 0.21	6.23 ± 0.46	5.81 ± 0.40	5.62 ± 0.55	6.68 ± 0.49	5.81 ± 0.37
FGF-1	8.52 ± 0.07	8.38 ± 0.17	8.49 ± 0.30	**6.31 ± 0.10**[a]	**6.76 ± 0.24**[a]	**6.71 ± 0.13**[a]
FGF-2	12.49 ± 0.04	12.87 ± 0.19	12.36 ± 0.19	12.85 ± 0.22	13.41 ± 0.09	12.74 ± 0.06
FGF-21[b]	0.52 ± 0.03	0.35 ± 0.07	0.27 ± 0.003	0.52 ± 0.10	0.60 ± 0.08	**0.54 ± 0.14**[a]
TGF-β1	11.07 ± 0.07	11.38 ± 0.14	11.32 ± 0.09	10.59 ± 0.14	11.04 ± 0.08	10.79 ± 0.11
TGF-β2[b]	5.81 ± 0.26	6.43 ± 0.29	6.26 ± 0.19	6.03 ± 0.24	5.85 ± 0.15	5.87 ± 0.16
HGF	5.73 ± 0.51	4.99 ± 0.36	4.62 ± 0.20	**7.68 ± 0.34**[a]	5.86 ± 0.42	**6.36 ± 0.18**[a]
VEGF-A	13.16 ± 0.16	13.14 ± 0.24	12.94 ± 0.21	12.73 ± 0.15	13.17 ± 0.06	12.88 ± 0.1
VEGF-B	11.24 ± 0.06	11.24 ± 0.01	10.99 ± 0.08	11.06 ± 0.03	**10.87 ± 0.04**[a]	10.91 ± 0.1
VEGF-C	10.75 ± 0.11	10.9 ± 0.15	10.93 ± 0.14	**9.77 ± 0.14**[a]	**9.86 ± 0.23**[a]	**9.88 ± 0.15**[a]
VEGF-D[b]	3.24 ± 0.06	3.15 ± 0.08	3.48 ± 0.24	**5.76 ± 0.58**[a]	**3.80 ± 0.38**[a]	**4.65 ± 0.47**[a]
MCSF	12.35 ± 0.08	12.22 ± 0.13	12.27 ± 0.13	12.13 ± 0.08	11.84 ± 0.12	12.07 ± 0.06
ICAM-1	9.50 ± 0.21	9.32 ± 0.45	9.86 ± 0.25	**6.39 ± 0.27**[a]	**6.26 ± 0.31**[a]	**6.68 ± 0.36**[a]
Transcription factor						
PPARγ	6.72 ± 0.22	6.89 ± 0.20	6.08 ± 0.20	**8.70 ± 0.32**[a]	**8.17 ± 0.30**[a]	**7.98 ± 0.22**[a]
Lipid metabolism						
LPL	3.83 ± 0.03	3.97 ± 0.04	3.95 ± 0.03	**10.48 ± 0.53**[a]	**8.67 ± 0.87**[a]	**7.43 ± 1.15**[a]
ApoE	6.43 ± 0.33	5.64 ± 0.19	6.11 ± 0.21	**11.81 ± 0.54**[a]	**10.26 ± 0.64**[a]	**10.07 ± 0.72**[a]
FABP4	4.41 ± 0.06	4.48 ± 0.04	4.41 ± 0.04	**11.72 ± 0.62**[a]	**10.17 ± 1.01**[a]	**9.51 ± 0.83**[a]
HCNP	11.45 ± 0.06	11.43 ± 0.06	11.43 ± 0.04	11.67 ± 0.14	11.48 ± 0.06	11.55 ± 0.07
RBP4[b]	4.38 ± 0.23	4.35 ± 0.13	4.43 ± 0.26	**7.11 ± 0.57**[a]	**5.95 ± 0.67**[a]	5.27 ± 0.57
Extracellular matrix						
Laminin β1 subunit	13.04 ± 0.16	12.98 ± 0.18	13.30 ± 0.11	12.76 ± 0.08	12.91 ± 0.12	**12.81 ± 0.04**[a]
Laminin β2 subunit	14.64 ± 0.03	14.59 ± 0.04	14.57 ± 0.01	**14.02 ± 0.05**[a]	**14.07 ± 0.05**[a]	**14.08 ± 0.03**[a]
Laminin β3 subunit	7.74 ± 0.05	7.12 ± 0.20	7.04 ± 0.14	**9.40 ± 0.22**[a]	**8.76 ± 0.33**[a]	**8.82 ± 0.13**[a]
Collagen IV α1 chain	15.91 ± 0.12	16.45 ± 0.18	16.02 ± 0.29	**15.13 ± 0.11**[a]	**15.59 ± 0.22**[a]	**15.21 ± 0.27**[a]
Collagen IV α2 chain	15.76 ± 0.09	16.16 ± 0.12	15.84 ± 0.23	**14.87 ± 0.12**[a]	**15.27 ± 0.18**[a]	**15.00 ± 0.24**[a]
Procollagen C-endopeptidase enhancer	11.53 ± 0.07	11.44 ± 0.06	11.17 ± 0.03	**11.19 ± 0.09**[a]	**10.91 ± 0.18**[a]	**10.8 ± 0.09**[a]

[a] p_{adj} **< 0.05** vs respective preadipocytes.
[b] BaseMean < 100 copies.

2. THE PREADIPOCYTE — THE PRECURSOR FAT CELL

2.1. Isolation and *in vitro* differentiation of preadipocytes into adipocytes

Due to the lack of specific markers, it is difficult to identify preadipocyte populations *in vivo*, and they are poorly characterized in every kind of tissue. However, the exclusion of endothelial (CD31+) and immune (CD14+) cell contamination by FACS made it possible to isolate preadipocytes from any fat pad [1,18–20]. The isolated and purified preadipocytes are ideally free of immune cells and consequently negative for IL-1β production. Preadipocytes proliferate *in vitro*, and so the cells can be expanded under specific culture conditions [19]. The differentiation into adipocytes is slow and requires, among other things, the addition of insulin to the medium. During differentiation, preadipocytes cease proliferation and begin to store lipids and produce adiponectin (Table 1). The secretome and the reactivity to factors known to be increased in pre-diabetes and diabetes can be examined in both preadipocyte and adipocyte populations under well-defined *in vitro* conditions.

2.2. Diabetic environment activates cytokine and chemokine production in preadipocytes and adipocytes

In vitro preparations of human pancreatic preadipocytes and adipocytes produce cytokines such as IL-6 (encoded by IL6 gene), IL-8 (encoded by CXCL8), and MCP-1 (encoded by CCL2) [1]. Although IL6 and CXCL8 mRNA levels of adipocytes are lower than of

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preadipocytes (Table 1), substances abundant in plasma of obese prediabetic humans, e.g., fatty acids (palmitic acid) and the hepatokine fetuin-A, specifically stimulate the production of IL-6, IL-8 and MCP-1 in preadipocytes and adipocytes [1,23]. Growth hormone and adipokine production remain unchanged. The selective stimulation of the above-mentioned cytokines may trigger local inflammation by attracting monocytes which may then convert into proinflammatory tissue macrophages. These macrophages, in turn, impair preadipocyte differentiation [24]. In obese patients, insulin-resistant visceral adipose tissue expresses TNFα and IL-6 [25]. However, tissue macrophages — but not fat cells — are the major source of cytotoxic cytokines, such as IL-1β, TNFα, and IFNγ, which are widely used for *in vitro* induction of β-cell apoptosis [26—28].

Since palmitic acid and fetuin-A stimulate IL-6, IL-8, and MCP-1 production in both fat cells and islets, these chemokines may also influence β-cell function in a paracrine manner during the development of obesity-linked diabetes. In isolated human islets that presumably do not contain adipocytes, high levels of CCL2 transcripts were found, whereas levels of IL6 and CXCL8 mRNA were low [1]. Thus, fat cells accentuate local inflammation.

3. LOW GRADE TISSUE INFLAMMATION

3.1. The role of local MCP-1 production

Multiple studies have already examined the effects of IL-6, IL-8, and MCP-1 on insulin secretion, β-cell survival, proliferation and apoptotic cell death (Figure 2). The chemokine MCP-1 is secreted by islet cells and summons an infiltration of monocytes into islets [29]. This chemotactic activity of MCP-1 plays a crucial role in the rejection of islet transplants [29]. Tissue adipocytes also secrete MCP-1 and activate local inflammation [1,18]. In human pancreas, the number of CD68-positive cells of the monocyte lineage was increased in the neighborhood of adipocytes [1]. The key cytokine produced in CD68-positive cells is the cytotoxic interleukin IL-1β. *In vitro*, IL-1β is detected in isolated human islets and is associated with tissue macrophages [26,30]. In isolated islets IL-1β production is stimulated by lipopolysaccharide (LPS) or palmitic acid-induced toll-like receptor-4 (TLR4) activation [30—33]. To avoid isolation and *in vitro* artifacts, human islet tissue was collected by laser capture microdissection (LCM) and directly analyzed using microarray, RNAseq, and RT-PCR methods [1,34]. An *in situ* analysis did not reveal any significant change in IL-1β mRNA levels in islets from resected human pancreas with high fat cell infiltration [1]. The IL-1β mRNA levels in islet tissue from humans with and without diabetes were also uniformly low. These observations indicate that human islets from patients with T2DM lack cytotoxic M1-macrophages producing IL-1β. However, a diffusion of IL-1β from surrounding tissue into islets, which cannot be captured by transcriptomic analysis, is still possible. Surprisingly, the area of insulin positive cells determined using *in situ* immunohistological staining was unaltered both in pancreatic tissue with high level of adipocyte infiltration and in tissue from T2DM patients when compared to specimens of non-fatty and non-diabetic humans, respectively. This finding differs from observations made in T1DM pancreata [35]. Multiple *in vitro* observations provide evidence of a direct cytotoxic effect of IL-1β on β-cells [26,31,36—38]. Interestingly, besides the cytotoxic effect, which is more prominent *in vitro* when IL-1β is used in conjunction with IFNγ and TNFα, low inflammation and postprandial plasma concentrations of IL-1β stimulate insulin secretion [27,39—

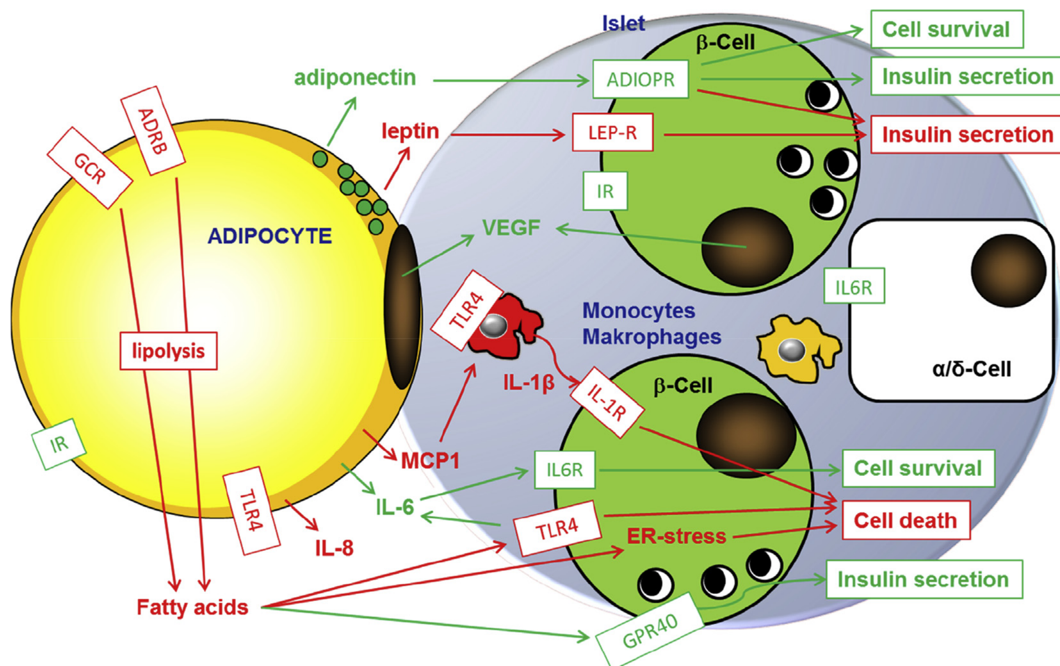

Figure 2: Effects of adipocyte derived factors on insulin secretion. In the neighborhood of islets adipocytes secrete adiponectin. By activating the adiponectin receptor 1 (ADIPOR) on β-cells, adiponectin stimulates insulin secretion and β-cell survival. Leptin, which is also produced by preadipocytes, inhibits insulin secretion via the leptin receptor activation (LEP-R). Via the glucagon receptor (GCR) and β-adrenergic receptors (ADRB), respectively, glucagon and adrenaline stimulate lipolysis in the adipocytes, resulting in a release of fatty acids. Fatty acids acutely stimulate insulin secretion through fatty acid receptor 1 (FFAR1/GPR40). Fatty acids induce ER stress when taken up chronically at high concentrations. This is associated with increased β-cell death. Fatty acids also activate the toll-like receptor 4 (TLR4) which is involved in β-cell death and inflammation. TLR4-dependent stimulation of MCP-1 and IL-8 exerts chemotactic effects on monocytes. TLR4 stimulation of tissue macrophages activates the release of the cytotoxic cytokine IL-1β and induces β-cell death.

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41]. To date, the provenance of cytokines is not understood and local, i.e., paracrine effects have not been studied in detail. Experiments with human pancreatic resections of variable fat content using the perifusion system presented by Marciniak et al. may help us to understand local effects of adipocytes on islet function and to examine the adipocyte secretome under defined conditions [42]. In conclusion, although inflammatory cytotoxicity plays an important role in β-cell loss in T1DM, its role in the development of T2DM, which has been proposed, requires further experimental evidence.

3.2. IL-6 and IL-8: good guys or bad guys?

The role of IL-6 in metabolism is not yet completely understood [43]. During exercise, IL-6 is released from muscle cells in great quantities and circulating IL-6 levels increase 50—100-fold [44]. Type 2 diabetes is associated with only a 2—4-fold elevation of circulating IL-6 levels compared to non-diabetic humans [45,46]. A massive release of IL-6 from exercising muscle increases insulin sensitivity through direct action on insulin receptor signaling [44,47]. By contrast, in hepatocytes, IL-6 has been reported to induce insulin resistance [48,49]. IL-6 is also a known regulator of adipose homeostasis in obesity [50]. These contrasting effects of IL-6 may explain the minor effect of IL-6 deficiency on glucose homeostasis in mice [43,51].

In islets, a consistent stimulatory effect of IL-6 on insulin secretion has not been found [52,53]. In mice, hepatic overexpression of IL-6 improved glucose tolerance and led to an increase of glucose-stimulated insulin secretion (GSIS) [52]. The beneficial effect on glucose tolerance in mice can be explained at least in part by a stimulatory effect of IL-6 on GLP-1 secretion from intestinal cells [54]. A further effect of IL-6 was the protection against cytokine-induced cell death [55]. Recent studies suggest that IL-6 protects β-cells from oxidative stress through the stimulation of autophagy [56,57]. A β-cell-specific knockout of IL-6-receptor α (IL6RA) in mice exacerbated oxidative stress. Secretion of IL-6 from pancreatic adipocytes contributes to high local levels of the cytokine and favors β-cell protection. In glucagon-secreting α-cells, IL-6 treatment increased proliferation [54,58]. Inversely, IL-6 is also a pro-inflammatory cytokine which is secreted by M1 macrophages and which has regulatory properties on macrophage polarization [59—61]. The crosstalk of pancreatic adipocytes with macrophages and the role of a local production of IL-6 on islet function require further experimental evidence [62]. Together with IL-6, IL-8 production is stimulated via activation of TLR4 in human islets [63]. IL-8 derives from pancreatic α-cells and serves as a chemoattractant for monocytes [30]. In fact, IL-8 antibodies inhibited LPS-induced monocyte migration in human islets [63]. Unlike the putative pro-inflammatory role of IL-8 derived from islets, the duct cell-derived IL-8 has been attributed a pro-angiogenic role that may favor islet graft revascularization [64]. The pleiotropic and contrasting effects of IL-6 and IL-8 on islet function disqualify them as possible therapeutic targets in the treatment of β-cell dysfunction (Figure 2).

4. SECRETION OF GROWTH HORMONES, ANGIOGENIC, AND FIBROTIC FACTORS

Increased inflammation and ROS production lead to fibrosis and insufficient perfusion, both of which are hallmarks of long-term diabetes complications [65]. The situation in the pancreas, however, is not so clear. Architecture of islets is altered during late diabetes when large amyloid-like deposits can be visualized [66,67]. These extracellular matrix deposits are believed to contribute to the impairment of insulin secretion [68,69]. However, multiple *in vitro* studies have failed to provide a conclusive picture [70—72]. When examining pancreatic tissue, the architecture of adjacent islets varies from a normal to a heavily damaged appearance. Only a low percentage of islets display extracellular deposits. In addition, such damaged islets were detected in pancreatic resections in 4 out of 44 T2DM patients (unpublished observation). Whether amyloid or fibrotic deposits contribute to impaired insulin secretion remains to be verified. Fibrosis and vascularization may determine whether or not insulin reaches the blood stream rapidly and efficiently. Vascularization and islet function were studied by Berggren and Speier using the method of islet transplantation into the anterior eye chamber [73—76]. This approach allows the *in vivo* visualization of islet architecture and function through the eye cornea. The formation of vessels within the engrafted islets of old mice into young mice improved insulin secretion and glucose homeostasis, suggesting that fibrosis of old islets hampers insulin disposition [76]. Vessel formation within the islets, as well as β-cell differentiation and function depend on the presence of VEGF-A since reduced vascularization and insulin production and secretion has been observed in the absence of VEGF-A [77]. However, both human islets and adipocytes produce VEGF to facilitate the maintenance of sufficient vascularization regardless of the degree of fat cells abundance (Table 1 and [1]). Furthermore, the secretion of growth factors from adipocytes, such as VEGF and HGF, remained unaffected by fatty acids and fetuin-A [1]. There is, therefore, no evidence that adipocytes disturb islet vascularization in humans. However, inflammation is accompanied by fibrosis in GK rats [78]. Whether locally released chemokines and cytokines from adipocytes contribute to inflammation and fibrotic tissue alterations and impact on vessel formation and *in vivo* hormone dissemination is still a matter of speculation.

5. CROSSTALK BETWEEN PANCREATIC ADIPOCYTES AND ISLETS

5.1. Effects of adipocytes on β-cell differentiation and function

The direct crosstalk between pancreatic adipocytes and islets has not yet been studied in depth [1,79]. Using the insulin secreting cell line Min6 and 3T3-L1 adipocytes in a co-culture system, a downregulation of glucokinase, of the K_{ATP}-channel protein Kir6.2, and of insulin has been observed [79]. *In vitro* exposure of human islets to preadipocytes and adipocytes in a co-culture system revealed that mRNA levels of islet differentiation markers (islet specific hormones, PDX-1 and GLUT-2) did not change [1]. The theory that fat cells do not affect β-cell differentiation is further corroborated by the unaltered *in situ* immunostaining for insulin, glucagon, and somatostatin of islets in the neighborhood of fat cells. Of note, this method may not be sensitive enough to detect changes of hormone storage until the reduction is already well advanced. Hormone content, moreover, may not correlate with the ability to secrete insulin in response to glucose. The use of new techniques such as metabolome and transcriptome analyses will provide additional information on changes induced by fatty degeneration of the pancreas as performed in subcutaneous fat biopsies [80].

5.2. Direct effects of leptin and adiponectin on islet function

Fat cells produce and secrete the hormones leptin and adiponectin [81,82]. Our parallel analysis of preadipocytes and adipocytes reveal that preadipocytes synthesize leptin while adiponectin production is induced upon differentiation into adipocytes only. Direct effects of leptin and adiponectin on insulin secretion and β-cell survival have been studied using *in vitro* systems and are summarized in several reviews as well as in Figure 2 [83—87]. Leptin signaling is linked to increased potassium channel activity through Jak2-dependent activation of AMPK and PI3K signaling pathways [88—90]. The underlying

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mechanism involves NMDA receptors and AMPK activation [91,92]. Furthermore, leptin-induced inhibition of GSIS is also linked to PKA activity and to an activation of phosphodiesterase PDE3B in both rodent and human islets [93,94]. A neuronal effect of leptin in the CNS may indirectly regulate insulin secretion [95]. The expression of leptin and adiponectin receptors has been demonstrated in both rodent and human islets [96,97]. In isolated single islet cells and purified β-cells, high expression of ADIPOR1 — but only a low expression of LEPR — was detected [98]. However, the role of adiponectin on insulin secretion is less clear since both stimulatory and inhibitory effects have been demonstrated [99—101]. The main action of adiponectin on β-cells would appear to be an anti-apoptotic effect through activation of AMPK [102—104]. We ascertained that neither leptin nor adiponectin secretion was stimulated by fatty acids and fetuin-A [1]. In humans with impaired glucose tolerance, fetuin-A was associated with reduced insulin secretion, whereas adiponectin was not [23]. The direct local effect of adiponectin and leptin secreted from pancreatic adipocytes and preadipocytes on islet function requires further experimental evidence.

5.3. Local effects of lipogenesis and lipolysis

Adipocytes store triglycerides in a large central lipid droplet. The vicinity of adipocytes to pancreatic islets may increase local concentrations of fatty acids in situations of increased lipolysis, but may reduce local fatty acid disposition under situations of lipogenesis. While insulin promotes lipogenesis, sympathetic stimulation through β-adrenergic receptors and fasting conditions activate lipolysis, resulting in a local elevation of fatty acids [105]. Fatty acids rapidly augment GSIS in dogs and rodents [106—110]. In humans, fatty acids stimulate insulin secretion even in the presence of low, non-stimulatory glucose concentrations [111]. Chronically elevated fatty acids, however, impair β-cell function, mainly by cytotoxic effects i.e., the promotion of apoptotic cell death [112,113]. The mechanism of lipotoxicity has been largely elucidated [114—121]. Most studies suggest that saturated fatty acids induce, while unsaturated inhibit β-cell death [114,115,122,123]. Of note, no more than 10—20% of the fatty acids released from adipocytes during lipolysis are saturated, the major part consisting of both mono- and polyunsaturated acids [124]. Lipolysis is induced by the activation of the β-adrenergic receptor expressed on the adipocyte plasma membrane [125]. Thus, on the one hand, sympathetic activation promotes lipolysis. On the other hand, (nor) adrenaline potently inhibits insulin secretion in both humans and rodents [126—128]. The inhibition of insulin secretion may further accentuate lipolysis since the latter is no longer inhibited by insulin. While the stimulation of lipolysis is exerted through β-adrenoceptors, the inhibition of insulin secretion is mediated via α_2-adrenoceptors and accompanied by a reduction in cytosolic Ca^{2+} and cAMP [129,130]. The α_2-adrenoceptors are expressed in β-cells, and a receptor polymorphism affects insulin secretion [15,131]. It has been proposed that the inhibitory effect on insulin secretion in humans is mediated only through the α_2-adrenoceptors expressed in endothelial cells, i.e., by reducing blood supply/flow. In human pseudoislets deprived of endothelial cells, adrenaline inhibits insulin secretion induced by glucose, GLP-1, and fatty acids, again pointing to a direct effect of adrenaline on the β-cell (E. Lorza Gil and S. Ullrich, submitted for publication).

Thus, the crosstalk between pancreatic adipocytes and islets is determined by the metabolic status which modulates both the secretome of adipocytes and islet function and, consequently, the putative paracrine effects (Figure 2).

From a β-cell point of view, hyperglycemia develops when the β-cell response is already impaired. High glucose is therefore not the primary cause but rather a consequence of β-cell failure [34,112,132]. Later during diabetes progression, persistent hyperglycemia exerts additional glucotoxic effects [68,133].

Under fasting conditions and under sympathetic activation, i.e. conditions of suppressed insulin secretion, locally stimulated lipolysis may increase fatty acid concentration within the tissue and augment insulin secretion [105]. Whether systemically high fatty acid concentrations or locally secreted fatty acids from neighboring adipocytes play the key role in insulin hypersecretion, which is observed in early stages of diabetes pathogenesis, remains elusive [134].

Multiple studies suggest that long term exposure to fatty acids exhausts β-cells by inducing chronic insulin hypersecretion and impairing insulin biosynthesis [135—140]. This deprives the cells of insulin, and, as a consequence, reduced and insufficient insulin secretion favors hyperglycemic episodes. Fatty acid-dependent insulin hypersecretion, therefore, could be one cause of relative insulin deficiency, a hallmark of T2DM. The lipotoxic effect of chronically elevated fatty acids is generally believed to reduce the functional β-cell mass, which explains at least in part the relative insulin deficiency in obesity-linked T2DM [133]. An analysis of islet architecture in human pancreatic resections showed heterogeneous islet size and highly variable staining for insulin, glucagon and somatostatin, regardless of diabetic status [1]. This high variability and the low number of damaged islets i.e., with extracellular deposits and a lower number of endocrine cells, make it difficult to exactly quantify β-cell mass using human pancreatic resections.

6. SUMMARY AND PERSPECTIVES

In summary, the secretome of adipocytes within the pancreas is regulated by the metabolic status, e.g., diabetogenic substances, and becomes adverse only upon induction of production and secretion of metabolites, chemokines, and interleukins. Increased uptake of fuels from local adipocytes may affect the local concentration of fatty acids as well as of glucose, all of which may have an impact on the stimulation of pancreatic endocrine cells. On the other hand, under conditions with increased lipolysis, a local accumulation of fatty acids may accentuate insulin secretion and chronically influence β-cell survival. Consequently, the locally produced and differentially secreted factors may initially influence β-cell function and, later in the disease development together with persistent hyperglycemia, also reduce β-cell mass. The effort to collect and characterize human pancreatic tissue specimens together with individual metabolic and genetic parameters will pave the way for a better understanding of changes within the human pancreas in the pathogenesis of diabetes. To date, it is not technically feasible to visualize and quantify paracrine effects. New sensitive methods are required with which small amounts of substances released locally can be visualized and measured.

ACKNOWLEDGMENTS

This study was supported by a grant (01GI0925) from the German Federal Ministry of Education and Research (BMBF) to the German Center for Diabetes Research (DZD e.V.). We gratefully acknowledge the excellent technical skills of Birgit Schreiner and Judith Nono (University Hospital Tübingen, Tübingen) for preadipocyte isolation and adipocyte differentiation.

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AUTHORS' CONTRIBUTIONS

SU, RW, and FG wrote the manuscript. HS and SU prepared the figures. MBO and DSA performed experiments and analyzed data of Table 1. HS, DSA, MH, AF, and HUH revised and corrected the manuscript.

CONFLICTS OF INTEREST

The authors declare no potential conflicts of interest.

REFERENCES

[1] Gerst, F., Wagner, R., Kaiser, G., Panse, M., Heni, M., Machann, J., et al., 2017. Metabolic crosstalk between fatty pancreas and fatty liver: effects on local inflammation and insulin secretion. Diabetologia 60(11):2240—2251.

[2] Czech, M.P., 2017. Insulin action and resistance in obesity and type 2 diabetes. Nature Medicine 23(7):804—814.

[3] Verma, S., Hussain, M.E., 2017. Obesity and diabetes: an update. Diabetes & Metabolic Syndrome 11(1):73—79.

[4] Stefan, N., Schick, F., Häring, H.U., 2017. Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. Cell Metabolism 26(2):292—300.

[5] Fraulob, J.C., Ogg-Diamantino, R., Fernandes-Santos, C., Aguila, M.B., Mandarim-de-Lacerda, C.A., 2010. A mouse model of metabolic syndrome: insulin resistance, fatty liver and non-alcoholic fatty pancreas disease (NAFPD) in C57BL/6 mice fed a high fat diet. Journal of Clinical Biochemistry and Nutrition 46(3):212—223.

[6] Pinnick, K.E., Collins, S.C., Londos, C., Gauguier, D., Clark, A., Fielding, B.A., 2008. Pancreatic ectopic fat is characterized by adipocyte infiltration and altered lipid composition. Obesity 16(3):522—530.

[7] Ogilvie, R.F., 1933. The islands of Langerhans in 19 cases of obesity. Journal of Pathology 37:473—481.

[8] Heni, M., Machann, J., Staiger, H., Schwenzer, N.F., Peter, A., Schick, F., et al., 2010. Pancreatic fat is negatively associated with insulin secretion in individuals with impaired fasting glucose and/or impaired glucose tolerance: a nuclear magnetic resonance study. Diabetes Metabolism Research and Reviews 26(3):200—205.

[9] Staaf, J., Labmayr, V., Paulmichl, K., Manell, H., Cen, J., Ciba, I., et al., 2017. Pancreatic fat is associated with metabolic syndrome and visceral fat but not beta-cell function or body mass index in pediatric obesity. Pancreas 46(3): 358—365.

[10] Nowotny, B., Kahl, S., Kluppelholz, B., Hoffmann, B., Giani, G., Livingstone, R., et al., 2018. Circulating triacylglycerols but not pancreatic fat associate with insulin secretion in healthy humans. Metabolism 81:113—125.

[11] Begovatz, P., Koliaki, C., Weber, K., Strassburger, K., Nowotny, B., Nowotny, P., et al., 2015. Pancreatic adipose tissue infiltration, parenchymal steatosis and beta cell function in humans. Diabetologia 58(7): 1646—1655.

[12] Catanzaro, R., Cuffari, B., Italia, A., Marotta, F., 2016. Exploring the metabolic syndrome: nonalcoholic fatty pancreas disease. World Journal of Gastroenterology 22(34):7660—7675.

[13] Smits, M.M., van Geenen, E.J., 2011. The clinical significance of pancreatic steatosis. Nature Reviews Gastroenterology & Hepatology 8(3):169—177.

[14] Guglielmi, V., Sbraccia, P., 2018. Type 2 diabetes: does pancreatic fat really matter? Diabetes Metabolism Research and Reviews 34(2) https://doi.org/10.1002/dmrr.2955.

[15] Rosengren, A.H., Jokubka, R., Tojjar, D., Granhall, C., Hansson, O., Li, D.Q., et al., 2010. Overexpression of alpha2A-adrenergic receptors contributes to type 2 diabetes. Science 327(5962):217—220.

[16] Dobbins, R.L., Szczepaniak, L.S., Myhill, J., Tamura, Y., Uchino, H., Giacca, A., et al., 2002. The composition of dietary fat directly influences glucose-stimulated insulin secretion in rats. Diabetes 51(6):1825—1833.

[17] Staiger, H., Häring, H.U., 2005. Adipocytokines: fat-derived humoral mediators of metabolic homeostasis. Experimental and Clinical Endocrinology & Diabetes 113(2):67—79.

[18] Rittig, K., Dolderer, J.H., Balletshofer, B., Machann, J., Schick, F., Meile, T., et al., 2012. The secretion pattern of perivascular fat cells is different from that of subcutaneous and visceral fat cells. Diabetologia 55(5):1514—1525.

[19] Siegel-Axel, D.I., Ullrich, S., Stefan, N., Rittig, K., Gerst, F., Klingler, C., et al., 2014. Fetuin-A influences vascular cell growth and production of proinflammatory and angiogenic proteins by human perivascular fat cells. Diabetologia 57(5):1057—1066.

[20] Siegel-Axel, D.I., Häring, H.U., 2016. Perivascular adipose tissue: an unique fat compartment relevant for the cardiometabolic syndrome. Reviews in Endocrine & Metabolic Disorders 17(1):51—60.

[21] Cawthorn, W.P., Scheller, E.L., MacDougald, O.A., 2012. Adipose tissue stem cells meet preadipocyte commitment: going back to the future. The Journal of Lipid Research 53(2):227—246.

[22] Sepe, A., Tchkonia, T., Thomou, T., Zamboni, M., Kirkland, J.L., 2011. Aging and regional differences in fat cell progenitors — a mini-review. Gerontology 57(1):66—75.

[23] Stefan, N., Sun, Q., Fritsche, A., Machann, J., Schick, F., Gerst, F., et al., 2014. Impact of the adipokine adiponectin and the hepatokine fetuin-A on the development of type 2 diabetes: prospective cohort- and cross-sectional phenotyping studies. PLoS One 9(3):e92238.

[24] Liu, L.F., Craig, C.M., Tolentino, L.L., Choi, O., Morton, J., Rivas, H., et al., 2017. Adipose tissue macrophages impair preadipocyte differentiation in humans. PLoS One 12(2):e0170728.

[25] Kern, P.A., Ranganathan, S., Li, C., Wood, L., Ranganathan, G., 2001. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. American Journal of Physiology Endocrinology and Metabolism 280(5):E745—E751.

[26] Maedler, K., Storling, J., Sturis, J., Zuellig, R.A., Spinas, G.A., Arkhammar, P.O., et al., 2004. Glucose- and interleukin-1beta-induced beta-cell apoptosis requires Ca2+ influx and extracellular signal-regulated kinase (ERK) 1/2 activation and is prevented by a sulfonylurea receptor 1/inwardly rectifying K+ channel 6.2 (SUR/Kir6.2) selective potassium channel opener in human islets. Diabetes 53(7):1706—1713.

[27] Dror, E., Dalmas, E., Meier, D.T., Wueest, S., Thevenet, J., Thienel, C., et al., 2017. Postprandial macrophage-derived IL-1beta stimulates insulin, and both synergistically promote glucose disposal and inflammation. Nature Immunology 18(3):283—292.

[28] Dinarello, C.A., Donath, M.Y., Mandrup-Poulsen, T., 2010. Role of IL-1beta in type 2 diabetes. Current Opinion in Endocrinology Diabetes and Obesity 17(4): 314—321.

[29] Piemonti, L., Leone, B.E., Nano, R., Saccani, A., Monti, P., Maffi, P., et al., 2002. Human pancreatic islets produce and secrete MCP-1/CCL2: relevance in human islet transplantation. Diabetes 51(1):55—65.

[30] Ehses, J.A., Perren, A., Eppler, E., Ribaux, P., Pospisilik, J.A., Maor-Cahn, R., et al., 2007. Increased number of islet-associated macrophages in type 2 diabetes. Diabetes 56(9):2356—2370.

[31] Maedler, K., Sergeev, P., Ris, F., Oberholzer, J., Joller-Jemelka, H.I., Spinas, G.A., et al., 2017. Glucose-induced beta cell production of IL-1beta contributes to glucotoxicity in human pancreatic islets. Journal of Clinical Investigation 127(4):1589. https://doi.org/10.1172/JCI92172.

[32] Ehses, J.A., Meier, D.T., Wueest, S., Rytka, J., Boller, S., Wielinga, P.Y., et al., 2010. Toll-like receptor 2-deficient mice are protected from insulin resistance and beta cell dysfunction induced by a high-fat diet. Diabetologia 53(8): 1795—1806.

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[33] Donath, M.Y., Boni-Schnetzler, M., Ellingsgaard, H., Ehses, J.A., 2009. Islet inflammation impairs the pancreatic beta-cell in type 2 diabetes. Physiology 24:325—331.

[34] Solimena, M., Schulte, A.M., Marselli, L., Ehehalt, F., Richter, D., Kleeberg, M., et al., 2018. Systems biology of the IMIDIA biobank from organ donors and pancreatectomised patients defines a novel transcriptomic signature of islets from individuals with type 2 diabetes. Diabetologia 61(3): 641—657.

[35] Mandrup-Poulsen, T., Pickersgil, L., Donath, M.Y., 2010. Blockade of interleukin 1 in type 1 diabetes mellitus. Nature Reviews Endocrinology 6(3):158—166.

[36] Cetkovic-Cvrlje, M., Eizirik, D.L., 1994. TNF-alpha and IFN-gamma potentiate the deleterious effects of IL-1 beta on mouse pancreatic islets mainly via generation of nitric oxide. Cytokine 6(4):399—406.

[37] Eizirik, D.L., Sandler, S., Welsh, N., Cetkovic-Cvrlje, M., Nieman, A., Geller, D.A., et al., 1994. Cytokines suppress human islet function irrespective of their effects on nitric oxide generation. Journal of Clinical Investigation 93(5):1968—1974.

[38] Wu, J.J., Chen, X., Cao, X.C., Baker, M.S., Kaufman, D.B., 2001. Cytokine-induced metabolic dysfunction of MIN6 beta cells is nitric oxide independent. Journal of Surgical Research 101(2):190—195.

[39] Spinas, G.A., Mandrup-Poulsen, T., Molvig, J., Baek, L., Bendtzen, K., Dinarello, C.A., et al., 1986. Low concentrations of interleukin-1 stimulate and high concentrations inhibit insulin release from isolated rat islets of Langerhans. Acta Endocrinologica 113(4):551—558.

[40] Jeong, I.K., Oh, S.H., Chung, J.H., Min, Y.K., Lee, M.S., Lee, M.K., et al., 2002. The stimulatory effect of IL-1beta on the insulin secretion of rat pancreatic islet is not related with iNOS pathway. Experimental & Molecular Medicine 34(1):12—17.

[41] Arous, C., Ferreira, P.G., Dermitzakis, E.T., Halban, P.A., 2015. Short term exposure of beta cells to low concentrations of interleukin-1beta improves insulin secretion through focal adhesion and actin remodeling and regulation of gene expression. Journal of Biological Chemistry 290(10):6653—6669.

[42] Marciniak, A., Cohrs, C.M., Tsata, V., Chouinard, J.A., Selck, C., Stertmann, J., et al., 2014. Using pancreas tissue slices for in situ studies of islet of Langerhans and acinar cell biology. Nature Protocols 9(12):2809—2822.

[43] Mauer, J., Denson, J.L., Brüning, J.C., 2015. Versatile functions for IL-6 in metabolism and cancer. Trends in Immunology 36(2):92—101.

[44] Pedersen, B.K., Fischer, C.P., 2007. Beneficial health effects of exercise — the role of IL-6 as a myokine. Trends in Pharmacological Sciences 28(4): 152—156.

[45] Herder, C., Haastert, B., Müller-Scholze, S., Koenig, W., Thorand, B., Holle, R., et al., 2005. Association of systemic chemokine concentrations with impaired glucose tolerance and type 2 diabetes: results from the Cooperative Health Research in the Region of Augsburg Survey S4 (KORA S4). Diabetes 54(Suppl. 2):S11—S17.

[46] Spranger, J., Kroke, A., Mohlig, M., Hoffmann, K., Bergmann, M.M., Ristow, M., et al., 2003. Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. Diabetes 52(3): 812—817.

[47] Hoene, M., Weigert, C., 2008. The role of interleukin-6 in insulin resistance, body fat distribution and energy balance. Obesity Reviews 9(1):20—29.

[48] Fuster, J.J., Walsh, K., 2014. The good, the bad, and the ugly of interleukin-6 signaling. EMBO Journal 33(13):1425—1427.

[49] Sabio, G., Das, M., Mora, A., Zhang, Z., Jun, J.Y., Ko, H.J., et al., 2008. A stress signaling pathway in adipose tissue regulates hepatic insulin resistance. Science 322(5907):1539—1543.

[50] Wueest, S., Konrad, D., 2018. The role of adipocyte-specific IL-6-type cytokine signaling in FFA and leptin release. Adipocyte 7(3):226—228.

[51] Fritsche, L., Hoene, M., Lehmann, R., Ellingsgaard, H., Hennige, A.M., Pohl, A.K., et al., 2010. IL-6 deficiency in mice neither impairs induction of metabolic genes in the liver nor affects blood glucose levels during fasting and moderately intense exercise. Diabetologia 53(8):1732—1742.

[52] Suzuki, T., Imai, J., Yamada, T., Ishigaki, Y., Kaneko, K., Uno, K., et al., 2011. Interleukin-6 enhances glucose-stimulated insulin secretion from pancreatic beta-cells: potential involvement of the PLC-IP3-dependent pathway. Diabetes 60(2):537—547.

[53] Sandler, S., Bendtzen, K., Eizirik, D.L., Welsh, M., 1990. Interleukin-6 affects insulin secretion and glucose metabolism of rat pancreatic islets in vitro. Endocrinology 126(2):1288—1294.

[54] Ellingsgaard, H., Hauselmann, I., Schuler, B., Habib, A.M., Baggio, L.L., Meier, D.T., et al., 2011. Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells. Nature Medicine 17(11):1481—1489.

[55] Choi, S.E., Choi, K.M., Yoon, I.H., Shin, J.Y., Kim, J.S., Park, W.Y., et al., 2004. IL-6 protects pancreatic islet beta cells from pro-inflammatory cytokines-induced cell death and functional impairment in vitro and in vivo. Transplant Immunology 13(1):43—53.

[56] Marasco, M.R., Conteh, A.M., Reissaus, C.A., Cupit, J.E., Appleman, E.M., Mirmira, R.G., et al., 2018. Interleukin-6 reduces beta-cell oxidative stress by linking autophagy with the antioxidant response. Diabetes 67(8): 1576—1588.

[57] Linnemann, A.K., Blumer, J., Marasco, M.R., Battiola, T.J., Umhoefer, H.M., Han, J.Y., et al., 2017. Interleukin 6 protects pancreatic beta cells from apoptosis by stimulation of autophagy. FASEB Journal 31(9):4140—4152.

[58] Ellingsgaard, H., Ehses, J.A., Hammar, E.B., Van Lommel, L., Quintens, R., Martens, G., et al., 2008. Interleukin-6 regulates pancreatic alpha-cell mass expansion. Proceedings of the National Academy of Sciences of the United States of America 105(35):13163—13168.

[59] Sarvari, A.K., Doan-Xuan, Q.M., Bacso, Z., Csomos, I., Balajthy, Z., Fesus, L., 2015. Interaction of differentiated human adipocytes with macrophages leads to trogocytosis and selective IL-6 secretion. Cell Death & Disease 6:e1613.

[60] Yasukawa, H., Ohishi, M., Mori, H., Murakami, M., Chinen, T., Aki, D., et al., 2003. IL-6 induces an anti-inflammatory response in the absence of SOCS3 in macrophages. Nature Immunology 4(6):551—556.

[61] Mauer, J., Chaurasia, B., Goldau, J., Vogt, M.C., Ruud, J., Nguyen, K.D., et al., 2014. Signaling by IL-6 promotes alternative activation of macrophages to limit endotoxemia and obesity-associated resistance to insulin. Nature Immunology 15(5):423—430.

[62] Morris, D.L., 2015. Minireview: emerging concepts in islet macrophage biology in type 2 diabetes. Molecular Endocrinology 29(7):946—962.

[63] He, W., Rebello, O., Savino, R., Terracciano, R., Schuster-Klein, C., Guardiola, B., et al., 2018. TLR4 triggered complex inflammation in human pancreatic islets. Biochimica et Biophysica Acta — Molecular Basis of Disease 1865(1):86—97.

[64] Movahedi, B., Gysemans, C., Jacobs-Tulleneers-Thevissen, D., Mathieu, C., Pipeleers, D., 2008. Pancreatic duct cells in human islet cell preparations are a source of angiogenic cytokines interleukin-8 and vascular endothelial growth factor. Diabetes 57(8):2128—2136.

[65] Ban, C.R., Twigg, S.M., 2008. Fibrosis in diabetes complications: pathogenic mechanisms and circulating and urinary markers. Vascular Health and Risk Management 4(3):575—596.

[66] Haataja, L., Gurlo, T., Huang, C.J., Butler, P.C., 2008. Islet amyloid in type 2 diabetes, and the toxic oligomer hypothesis. Endocrine Reviews 29(3):303—316.

[67] Lorenzo, A., Razzaboni, B., Weir, G.C., Yankner, B.A., 1994. Pancreatic islet cell toxicity of amylin associated with type-2 diabetes mellitus. Nature 368: 756—760.

[68] Wajchenberg, B.L., 2007. beta-cell failure in diabetes and preservation by clinical treatment. Endocrine Reviews 28(2):187—218.

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[69] Bennett, R.G., Hamel, F.G., Duckworth, W.C., 2003. An insulin-degrading enzyme inhibitor decreases amylin degradation, increases amylin-induced cytotoxicity, and increases amyloid formation in insulinoma cell cultures. Diabetes 52(9):2315—2320.

[70] Silvestre, R.A., Salas, M., García-Hermida, O., Fontela, T., Dégano, P., Marco, J., 1994. Amylin (islet amyloid polypeptide) inhibition of insulin release in the perfused rat pancreas: implication of the adenylate cyclase/ cAMP system. Regulatory Peptides 50:193—199.

[71] Ritzel, R.A., Butler, P.C., 2003. Replication increases beta-cell vulnerability to human islet amyloid polypeptide-induced apoptosis. Diabetes 52(7): 1701—1708.

[72] Mirzabekov, T.A., Lin, M.C., Kagan, B.L., 1996. Pore formation by the cytotoxic islet amyloid peptide amylin. Journal of Biological Chemistry 271(4): 1988—1992.

[73] Cohrs, C.M., Chen, C., Jahn, S.R., Stertmann, J., Chmelova, H., Weitz, J., et al., 2017. Vessel network architecture of adult human islets promotes distinct cell—cell interactions in situ and is altered after transplantation. Endocrinology 158(5):1373—1385.

[74] Ilegems, E., Dicker, A., Speier, S., Sharma, A., Bahow, A., Edlund, P.K., et al., 2013. Reporter islets in the eye reveal the plasticity of the endocrine pancreas. Proceedings of the National Academy of Sciences of the United States of America 110(51):20581—20586.

[75] Speier, S., Nyqvist, D., Kohler, M., Caicedo, A., Leibiger, I.B., Berggren, P.O., 2008. Noninvasive high-resolution in vivo imaging of cell biology in the anterior chamber of the mouse eye. Nature Protocols 3(8):1278—1286.

[76] Almaca, J., Molina, J., Arrojo, E.D.R., Abdulreda, M.H., Jeon, W.B., Berggren, P.O., et al., 2014. Young capillary vessels rejuvenate aged pancreatic islets. Proceedings of the National Academy of Sciences of the United States of America 111(49):17612—17617.

[77] Jabs, N., Franklin, I., Brenner, M.B., Gromada, J., Ferrara, N., Wollheim, C.B., et al., 2008. Reduced insulin secretion and content in VEGF-a deficient mouse pancreatic islets. Experimental and Clinical Endocrinology & Diabetes 116(1):S46—S49.

[78] Homo-Delarche, F., Calderari, S., Irminger, J.C., Gangnerau, M.N., Coulaud, J., Rickenbach, K., et al., 2006. Islet inflammation and fibrosis in a spontaneous model of type 2 diabetes, the GK rat. Diabetes 55(6): 1625—1633.

[79] Zhao, Y.F., Feng, D.D., Hernandez, M., Chen, C., 2007. 3T3-L1 adipocytes induce dysfunction of MIN6 insulin-secreting cells via multiple pathways mediated by secretory factors in a co-culture system. Endocrine 31(1): 52—60.

[80] Gerlini, R., Berti, L., Darr, J., Lassi, M., Brandmaier, S., Fritsche, L., et al., 2018. Glucose tolerance and insulin sensitivity define adipocyte transcriptional programs in human obesity. Molecular Metabolism 18:42—50.

[81] Komai, A.M., Musovic, S., Peris, E., Alrifaiy, A., El Hachmane, M.F., Johansson, M., et al., 2016. White adipocyte adiponectin exocytosis is stimulated via beta3-adrenergic signaling and activation of Epac1: catecholamine resistance in obesity and type 2 diabetes. Diabetes 65(11): 3301—3313.

[82] Stern, J.H., Rutkowski, J.M., Scherer, P.E., 2016. Adiponectin, leptin, and fatty acids in the maintenance of metabolic homeostasis through adipose tissue crosstalk. Cell Metabolism 23(5):770—784.

[83] Lee, Y.H., Magkos, F., Mantzoros, C.S., Kang, E.S., 2011. Effects of leptin and adiponectin on pancreatic beta-cell function. Metabolism 60(12):1664—1672.

[84] Dunmore, S.J., Brown, J.E., 2013. The role of adipokines in beta-cell failure of type 2 diabetes. Journal of Endocrinology 216(1):T37—T45.

[85] Zhao, Y.F., Feng, D.D., Chen, C., 2006. Contribution of adipocyte-derived factors to beta-cell dysfunction in diabetes. The International Journal of Biochemistry & Cell Biology 38(5—6):804—819.

[86] Kulkarni, R.N., Wang, Z.L., Wang, R.M., Hurley, J.D., Smith, D.M., Ghatei, M.A., et al., 1997. Leptin rapidly suppresses insulin release from insulinoma cells, rat and human islets and, in vivo, in mice. Journal of Clinical Investigation 100(11):2729—2736.

[87] Fehmann, H.C., Peiser, C., Bode, H.P., Stamm, M., Staats, P., Hedetoft, C., et al., 1997. Leptin: a potent inhibitor of insulin secretion. Peptides 18(8): 1267—1273.

[88] Park, S.H., Ryu, S.Y., Yu, W.J., Han, Y.E., Ji, Y.S., Oh, K., et al., 2013. Leptin promotes K(ATP) channel trafficking by AMPK signaling in pancreatic beta-cells. Proceedings of the National Academy of Sciences of the United States of America 110(31):12673—12678.

[89] Kieffer, T.J., Heller, R.S., Leech, C.A., Holz, G.G., Habener, J.F., 1997. Leptin suppression of insulin secretion by the activation of ATP-sensitive K+ channels in pancreatic beta-cells. Diabetes 46(6):1087—1093.

[90] Harvey, J., Hardy, S.C., Irving, A.J., Ashford, M.L., 2000. Leptin activation of ATP-sensitive K+ (KATP) channels in rat CRI-G1 insulinoma cells involves disruption of the actin cytoskeleton. Journal of Physiology 527(Pt 1):95—107.

[91] Wu, Y., Shyng, S.L., Chen, P.C., 2015. Concerted trafficking regulation of Kv2.1 and KATP channels by leptin in pancreatic beta-cells. Journal of Biological Chemistry 290(50):29676—29690.

[92] Wu, Y., Fortin, D.A., Cochrane, V.A., Chen, P.C., Shyng, S.L., 2017. NMDA receptors mediate leptin signaling and regulate potassium channel trafficking in pancreatic beta-cells. Journal of Biological Chemistry 292(37):15512—15524.

[93] Zhao, A.Z., Bornfeldt, K.E., Beavo, J.A., 1998. Leptin inhibits insulin secretion by activation of phosphodiesterase 3B. Journal of Clinical Investigation 102(5):869—873.

[94] Ahren, B., Havel, P.J., 1999. Leptin inhibits insulin secretion induced by cellular cAMP in a pancreatic B cell line (INS-1 cells). American Journal of Physiology 277(4):R959—R966.

[95] Muzumdar, R., Ma, X., Yang, X., Atzmon, G., Bernstein, J., Karkanias, G., et al., 2003. Physiologic effect of leptin on insulin secretion is mediated mainly through central mechanisms. FASEB Journal 17(9):1130—1132.

[96] Emilsson, V., Liu, Y.L., Cawthorne, M.A., Morton, N.M., Davenport, M., 1997. Expression of the functional leptin receptor mRNA in pancreatic islets and direct inhibitory action of leptin on insulin secretion. Diabetes 46(2):313—316.

[97] Kieffer, T.J., Heller, R.S., Habener, J.F., 1996. Leptin receptors expressed on pancreatic beta-cells. Biochemical and Biophysical Research Communications 224(2):522—527.

[98] Segerstolpe, A., Palasantza, A., Eliasson, P., Andersson, E.M., Andreasson, A.C., Sun, X., et al., 2016. Single-cell transcriptome profiling of human pancreatic islets in health and type 2 diabetes. Cell Metabolism 24(4): 593—607.

[99] Staiger, K., Stefan, N., Staiger, H., Brendel, M.D., Brandhorst, D., Bretzel, R.G., et al., 2005. Adiponectin is functionally active in human islets but does not affect insulin secretory function or beta-cell lipoapoptosis. Journal of Clinical Endocrinology and Metabolism 90(12):6707—6713.

[100] Rakatzi, I., Mueller, H., Ritzeler, O., Tennagels, N., Eckel, J., 2004. Adiponectin counteracts cytokine- and fatty acid-induced apoptosis in the pancreatic beta-cell line INS-1. Diabetologia 47(2):249—258.

[101] Okamoto, M., Ohara-Imaizumi, M., Kubota, N., Hashimoto, S., Eto, K., Kanno, T., et al., 2008. Adiponectin induces insulin secretion in vitro and in vivo at a low glucose concentration. Diabetologia 51(5):827—835.

[102] Wijesekara, N., Krishnamurthy, M., Bhattacharjee, A., Suhail, A., Sweeney, G., Wheeler, M.B., 2010. Adiponectin-induced ERK and Akt phosphorylation protects against pancreatic beta cell apoptosis and increases insulin gene expression and secretion. Journal of Biological Chemistry 285(44):33623—33631.

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[103] Spranger, J., Kroke, A., Mohlig, M., Bergmann, M.M., Ristow, M., Boeing, H., et al., 2003. Adiponectin and protection against type 2 diabetes mellitus. Lancet 361(9353):226–228.

[104] Lin, P., Chen, L., Li, D., Liu, J., Yang, N., Sun, Y., et al., 2009. Adiponectin reduces glucotoxicity-induced apoptosis of INS-1 rat insulin-secreting cells on a microfluidic chip. Tohoku Journal of Experimental Medicine 217(1):59–65.

[105] Bartness, T.J., Liu, Y., Shrestha, Y.B., Ryu, V., 2014. Neural innervation of white adipose tissue and the control of lipolysis. Frontiers in Neuroendocrinology 35(4):473–493.

[106] Crespin, S.R., Greenough III, W.B., Steinberg, D., 1973. Stimulation of insulin secretion by long-chain free fatty acids. A direct pancreatic effect. Journal of Clinical Investigation 52(8):1979–1984.

[107] Stein, D.T., Stevenson, B.E., Chester, M.W., Basit, M., Daniels, M.B., Turley, S.D., et al., 1997. The insulinotropic potency of fatty acids is influenced profoundly by their chain length and degree of saturation. Journal of Clinical Investigation 100(2):398–403.

[108] Briscoe, C.P., Tadayyon, M., Andrews, J.L., Benson, W.G., Chambers, J.K., Eilert, M.M., et al., 2003. The orphan G protein-coupled receptor GPR40 is activated by medium and long chain fatty acids. Journal of Biological Chemistry 278(13):11303–11311.

[109] Itoh, Y., Kawamata, Y., Harada, M., Kobayashi, M., Fujii, R., Fukusumi, S., et al., 2003. Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. Nature 422(6928):173–176.

[110] Latour, M.G., Alquier, T., Oseid, E., Tremblay, C., Jetton, T.L., Luo, J., et al., 2007. GPR40 is necessary but not sufficient for fatty acid stimulation of insulin secretion in vivo. Diabetes 56(4):1087–1094.

[111] Cen, J., Sargsyan, E., Bergsten, P., 2016. Fatty acids stimulate insulin secretion from human pancreatic islets at fasting glucose concentrations via mitochondria-dependent and -independent mechanisms. Nutrition & Metabolism 13(1):59. https://doi.org/10.1186/s12986-016-0119-5.

[112] Poitout, V., Robertson, R.P., 2008. Glucolipotoxicity: fuel excess and beta-cell dysfunction. Endocrine Reviews 29(3):351–366.

[113] Paolisso, G., Gambardella, A., Amato, L., Tortoriello, R., D'Amore, A., Varricchio, M., et al., 1995. Opposite effects of short- and long-term fatty acid infusion on insulin secretion in healthy subjects. Diabetologia 38(11):1295–1299.

[114] El Assaad, W., Buteau, J., Peyot, M.L., Nolan, C., Roduit, R., Hardy, S., et al., 2003. Saturated fatty acids synergize with elevated glucose to cause pancreatic beta-cell death. Endocrinology 144(9):4154–4163.

[115] Maedler, K., Oberholzer, J., Bucher, P., Spinas, G.A., Donath, M.Y., 2003. Monounsaturated fatty acids prevent the deleterious effects of palmitate and high glucose on human pancreatic beta-cell turnover and function. Diabetes 52(3):726–733.

[116] van Raalte, D.H., van der Zijl, N.J., Diamant, M., 2010. Pancreatic steatosis in humans: cause or marker of lipotoxicity? Current Opinion in Clinical Nutrition and Metabolic Care 13(4):478–485.

[117] Eizirik, D.L., Cardozo, A.K., Cnop, M., 2008. The role for endoplasmic reticulum stress in diabetes mellitus. Endocrine Reviews 29(1):42–61.

[118] Cnop, M., Ladriere, L., Igoillo-Esteve, M., Moura, R.F., Cunha, D.A., 2010. Causes and cures for endoplasmic reticulum stress in lipotoxic beta-cell dysfunction. Diabetes, Obesity & Metabolism 12(2):76–82.

[119] Eizirik, D.L., Cnop, M., 2010. ER stress in pancreatic beta cells: the thin red line between adaptation and failure. Science Signalling 3(110):pe7.

[120] Han, J., Kaufman, R.J., 2016. The role of ER stress in lipid metabolism and lipotoxicity. The Journal of Lipid Research 57(8):1329–1338.

[121] Biden, T.J., Boslem, E., Chu, K.Y., Sue, N., 2014. Lipotoxic endoplasmic reticulum stress, beta cell failure, and type 2 diabetes mellitus. Trends in Endocrinology and Metabolism 25(8):389–398.

[122] Eitel, K., Staiger, H., Brendel, M.D., Brandhorst, D., Bretzel, R.G., Häring, H.U., et al., 2002. Different role of saturated and unsaturated fatty acids in beta-cell apoptosis. Biochemical and Biophysical Research Communications 299(5):853–856.

[123] Eitel, K., Staiger, H., Rieger, J., Mischak, H., Brandhorst, H., Brendel, M.D., et al., 2003. Protein kinase C delta activation and translocation to the nucleus are required for fatty acid-induced apoptosis of insulin-secreting cells. Diabetes 52(4):991–997.

[124] Caron-Jobin, M., Mauvoisin, D., Michaud, A., Veilleux, A., Noel, S., Fortier, M.P., et al., 2012. Stearic acid content of abdominal adipose tissues in obese women. Nutrition & Diabetes 2:e23. https://doi.org/10.1038/nutd.2011.19.

[125] Frühbeck, G., Mendez-Gimenez, L., Fernandez-Formoso, J.A., Fernandez, S., Rodriguez, A., 2014. Regulation of adipocyte lipolysis. Nutrition Research Reviews 27(1):63–93.

[126] Ullrich, S., Wollheim, C.B., 1989. Characterization of alpha 2-adrenoceptors in a plasma membrane enriched fraction from the insulin-secreting cell line RINm5F. Acta Endocrinologica 121:525–532.

[127] Yamazaki, S., Katada, T., Ui, M., 1982. Alpha 2-adrenergic inhibition of insulin secretion via interference with cyclic AMP generation in rat pancreatic islets. Molecular Pharmacology 21:648–653.

[128] Peterhoff, M., Sieg, A., Brede, M., Chao, C.M., Hein, L., Ullrich, S., 2003. Inhibition of insulin secretion via distinct signaling pathways in alpha2-adrenoceptor knockout mice. European Journal of Endocrinology 149(4):343–350.

[129] Ullrich, S., Wollheim, C.B., 1984. Islet cyclic AMP levels are not lowered during alpha 2-adrenergic inhibition of insulin release. Journal of Biological Chemistry 259:4111–4115.

[130] Sieg, A., Su, J., Munoz, A., Buchenau, M., Nakazaki, M., Aguilar-Bryan, L., et al., 2004. Epinephrine-induced hyperpolarization of islet cells without KATP channels. American Journal of Physiology. Endocrinology and Metabolism 286(3):E463–E471.

[131] Renström, E., Ding, W., Bokvist, K., Rorsman, P., 1996. Neurotransmitter-induced inhibition of exocytosis in insulin-secreting b cells by activation of calcineurin. Neuron 17:513–522.

[132] Ahren, B., 2005. Type 2 diabetes, insulin secretion and beta-cell mass. Current Molecular Medicine 5(3):275–286.

[133] Marchetti, P., Lupi, R., Del Guerra, S., Bugliani, M., Marselli, L., Boggi, U., 2010. The beta-cell in human type 2 diabetes. Advances in Experimental Medicine & Biology 654:501–514.

[134] Trico, D., Natali, A., Arslanian, S., Mari, A., Ferrannini, E., 2018. Identification, pathophysiology, and clinical implications of primary insulin hypersecretion in nondiabetic adults and adolescents. JCI Insight 3(24):124912. https://doi.org/10.1172/jci.insight.124912.

[135] Zhou, Y.P., Grill, V.E., 1994. Long-term exposure of rat pancreatic islets to fatty acids inhibits glucose-induced insulin secretion and biosynthesis through a glucose fatty acid cycle. Journal of Clinical Investigation 93(2):870–876.

[136] Zhou, Y.P., Grill, V., 1995. Long term exposure to fatty acids and ketones inhibits B-cell functions in human pancreatic islets of Langerhans. Journal of Clinical Endocrinology & Metabolism 80(5):1584–1590.

[137] Ritz-Laser, B., Meda, P., Constant, I., Klages, N., Charollais, A., Morales, A., et al., 1999. Glucose-induced preproinsulin gene expression is inhibited by the free fatty acid palmitate. Endocrinology 140(9):4005–4014.

[138] Watson, M.L., Macrae, K., Marley, A.E., Hundal, H.S., 2011. Chronic effects of palmitate overload on nutrient-induced insulin secretion and autocrine signalling in pancreatic MIN6 beta cells. PLoS One 6(10):e25975.

[139] Wagner, R., Kaiser, G., Gerst, F., Christiansen, E., Due-Hansen, M.E., Grundmann, M., et al., 2013. Reevaluation of fatty acid receptor 1 as a drug target for the stimulation of insulin secretion in humans. Diabetes 62(6):2106–2111.

[140] Nolan, C.J., Madiraju, M.S., Delghingaro-Augusto, V., Peyot, M.L., Prentki, M., 2006. Fatty acid signaling in the beta-cell and insulin secretion. Diabetes 55(2):S16–S23.

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