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Plasma cells and Fc receptors in human adipose tissue—lipogenic and anti-inflammatory effects of immunoglobulins on adipocytes

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Abstract

We have previously reported high immunoglobulin expression in human omental adipose tissue. The aim of this work was to investigate plasma cell density and Fc receptor (FcR) expression in human adipose tissue depots and in vitro effects of immunoglobulins on adipocyte function. Plasma cell density was higher in the visceral compared to the subcutaneous depot ($10.0 \pm 1.56\%$ and $5.2 \pm 0.98\%$, respectively, $n = 20$, $p < 0.05$). Microarray analysis revealed expression of four FcR genes in adipose tissue; FCGR2A, FCGR2B, FCER1G, and FCGRT. FCGR2A was highly expressed in adipocytes in both depots and this was verified by immunohistochemistry. Expression of IL-1β and IL-6 was markedly reduced in adipocytes after incubation with the Fc moiety of immunoglobulin G (Fc) ($p < 0.01$). Furthermore, Fc stimulated adipocyte lipogenesis as potently as insulin ($p < 0.05$), but did not influence lipolysis. In conclusion, immunoglobulins produced by plasma cells in human adipose tissue could influence adipocyte metabolism and cytokine production.

Keywords: Adipocyte; Human; Plasma cell; Immunoglobulin; Fc receptor; Immunity; Visceral; Insulin; Cytokine; Lipogenesis

Obesity is associated with a state of chronic, low-grade inflammation [1]. Circulating levels of inflammatory markers are elevated in obese subjects, and adipose cells secrete several proinflammatory cytokines, chemokines, complement factors, and acute-phase proteins [2,3]. Moreover, adipokines such as leptin and adiponectin with documented metabolic functions can regulate the immune response [4,5]. Further support for an association between obesity and inflammation comes from studies showing macrophage infiltration of adipose tissue. Immunohistochemical analysis of human subcutaneous adipose tissue showed that macrophage accumulation was directly proportional to body mass index (BMI) and adipocyte size, both measures of adiposity [6].

Taken together, there appears to be a close interaction between metabolism and in particular, the innate immune system [1,7]. Less is known about involvement of the adaptive immunity in this context. However, in Pima Indians, serum levels of gamma globulins are positively correlated to BMI and predict risk of type 2 diabetes [8]. Energy restriction has been reported to decrease serum levels of immunoglobulins in overweight and obese subjects [9,10]. We have previously reported high expression of immunoglobulin (Ig) genes in omental adipose tissue in obese men [11]. Furthermore, Igs have been reported to stimulate lipogenesis, pointing to the presence of Fc receptors (FcR) on adipocytes [12]. To our knowledge, plasma cell density and FcR expression per se in human adipose tissue have not been investigated.

In the present study, we report that plasma cell density is higher in omental compared to subcutaneous adipose tissue

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of obese subjects. Furthermore, adipocytes express mainly the FcγRII receptor analyzed by microarray and immunohistochemistry, and the Fc moiety of IgG (Fc) attenuates interleukin (IL) expression and stimulates lipogenesis in human adipocytes in vitro.

Materials and methods

Subjects and samples. Abdominal adipose tissue from 38 subjects was obtained after an overnight fast. Both subcutaneous and omental biopsies were obtained from 20 subjects, 12 men/8 women, undergoing gastric bypass (BMI: 44.9 ± 1.9 kg/m^2; age: 41.6 ± 2.1 years). Subcutaneous samples were taken from eight subjects, 7 men/1 woman, undergoing gastric bypass or abdominoplasty (BMI: 47.6 ± 4.1 kg/m^2; age: 42.4 ± 3.6 years). Subcutaneous needle aspirations were obtained from 10 volunteers, 1 man/9 women (BMI: 29.6 ± 1.7 kg/m^2; age: 44.8 ± 2.4 years). Adipocytes were isolated from adipose tissue [13]. The study was approved by the Regional Ethical Review Board in Göteborg and all participants gave written informed consent.

Microarray analysis and tissue expression profiles. Gene expression in subcutaneous and omental adipose tissue from six obese men, and in corresponding adipocyte fractions from one of these subjects, was analyzed by microarray (HU95A arrays, Affymetrix, Santa Clara, CA) as previously described [14]. These expression profiles were compared to expression profiles of human macrophages [15] and publicly available expression profiles from several human tissues and cell types [16,17] as previously described [18].

Immunohistochemistry. Pieces of adipose tissue were fixed in buffered paraformaldehyde (4%), dehydrated, and embedded in paraffin using standard procedures. Four micrometer thick slices were prepared and incubated with a monoclonal antibody against plasma cells (clone VS38c, DakoCytomation, Glostrup, Denmark). Peroxidase anti-peroxidase was used as secondary reagent (DakoCytomation) and 3,3-diaminobenzidine/H_2O_2 as substrate. The sections were lightly counterstained with hematoxylin. The number of plasma cells and the total number of stroma-vascular nuclei in adipose tissue depots were counted in 20 visual fields at 20× magnification (total area 1.33 mm^2). The visual fields were randomly selected, but excluding major connective tissue streaks to avoid bias caused by the differences in cell composition of the two tissues [14]. Plasma cell density was expressed as number of plasma cells related to the total number of stroma-vascular nuclei in the same visual fields.

Freshly isolated adipocytes were mixed with Tissue-Tek (Sakura Finetek, Torrance, CA) and frozen in liquid nitrogen. Ten micrometer thick cryostat sections were fixed in cold acetone and air–dried prior to incubation with monoclonal CD32 antibody (DakoCytomation) to localize FcγRII receptors. The secondary steps and visualization were as described above.

Gene expression in incubated adipocytes. Subcutaneous adipocytes were diluted 10 times in MEM and incubated with or without Fc (600 μg/ml), insulin (1 μU/ml) or TNFα (20 ng/ml, Invitrogen) for 6 h at 37 °C in a gently shaking water bath. Total RNA was isolated from the adipocytes using the Lipid Tissue RNEasy Kit (Qiagen, Hilden, Germany). Gene expression of IL-1β, IL-6, TNFα, and PPIA was analyzed by real-time RT-PCR using assays-on-demand, TaqMan® Reverse Transcriptase reagents, TaqMan® Universal PCR Master mix (Applied Biosystems, Foster City, CA), following the manufacturer's instructions. Working standards were prepared from a large pool of adipocyte RNAs and standard cDNA was synthesized in parallel with the sample cDNAs. A standard curve, obtained by serial dilution of the standard cDNA (range 0.625 to 40 ng original RNA per well), was included on each plate. Amplification and detection of specific products were performed with the ABI PRISM® 7900HT Sequence Detection System (Applied Biosystems) using default cycle parameters. All standards and samples were analyzed in triplicate. PPIA was used as reference to normalize the expression levels between samples.

Lipogenesis. Triglyceride biosynthesis in isolated subcutaneous adipocytes was estimated by measurement of incorporated ^{14}C-glucose (final specific activity 0.07 μCi/μmol, Amersham, Buckinghamshire, UK) in triglycerides. Adipocytes were incubated in Parker medium (SBL, Stockholm, Sweden) supplemented with 4% BSA (fraction V, Sigma-Aldrich, St. Louis, MO) and ^{14}C-glucose (Amersham) at a total glucose concentration of 5.5 mM with or without insulin (Sigma-Aldrich, 1 μU/ml), Fc (Fc fragment of human IgG, Merck Biosciences, Darmstadt, Germany, 600 μg/ml), and the combination of insulin and Fc in a gently shaking water bath at 37 °C for 2 h. Lipid was extracted as described [19], and radioactivity was determined by scintillation counting.

Lipolysis. Lipolysis measurements were performed as described [20]. Subcutaneous adipocytes were incubated in MEM (Invitrogen, Carlsbad, CA) containing 5.5 mM glucose, 25 mM Hepes (pH 7.4), 4% BSA, and 0.15 μM adenosine with or without noradrenaline (10^{-5} M), noradrenaline/Fc (600 μg/ml), noradrenaline/insulin (insulin, 1 μU/ml), and noradrenaline/Fc/insulin in a gently shaking water bath at 37 °C for 2 h. The glycerol content of the medium was taken as an index of lipolysis expressed as nmol glycerol/10^4 cells. Fat cell size was determined according to Björnheden et al. [21].

Statistical analysis. Results are presented as mean ± standard error of the mean (SEM) unless otherwise stated. Comparisons were performed using Wilcoxon signed-rank test or Student's t test.

Results

Expression of immunoglobulins in adipose tissue

We have previously reported higher expression of the Ig genes, IGHG3, IGKC, and IGL@, in omental compared to subcutaneous adipose tissue from obese men [11]. In this study, we investigated adipose tissue and adipocyte expression of all Ig genes represented on the microarray, irrespective of whether they showed depot-specific expression or not (Table 1). In addition to the Ig genes mentioned above, IGHM and IGHA were also expressed in adipose tissue and as expected, no Ig genes were expressed in the adipocyte fraction (data not shown).

Plasma cells in adipose tissue

Plasma cells in paired biopsies of subcutaneous and omental adipose tissue from 20 obese subjects were detected by immunohistochemistry (Fig. 1A). On average, the plasma cell density, expressed as number of plasma cells related to the total number of stroma-vascular nuclei in the same visual fields, was twice as high in omental (range 2.9–29.4%; mean 10.0 ± 1.56 %) compared to subcutaneous (range 0.0–15.6%; mean 5.2 ± 0.98%) adipose tissue (Fig. 1B, $p < 0.05$).

Expression and detection of FcR in adipose tissue and adipocytes

Four FcR genes, FCGR2A, FCGR2B, FCER1G, and FCGRT, were detected in adipose tissue in at least four out of the six subjects according to the microarray data. FCGRT, highly expressed in adipose tissue and adipocytes, is involved in IgG transport [22]. FCER1G, a FcεR subunit, was detected at low levels, but FCER1A, another

Table 1
Relative expression of immunoglobulins in omental compared to subcutaneous adipose tissue in six obese men analyzed by microarray

Symbol	Gene name	Subject					
		1	2	3	4	5	6
IGHG3/IGHM*	Ig heavy chain gamma/Ig heavy chain mu	7.3 ± 1.0	5.5 ± 1.3	2.1 ± 0.9	3.0 ± 0.6	2.9 ± 1.1	20.9 ± 24.0
		1.9 ± 0.2	nd	1.2 ± 0.1	nd	nd	3.5 ± 3.9
IGHM	Ig heavy chain mu	nd	1.8 ± 0.4	1.9 ± 0.5	nd	nd	1.9 ± 0.5
		nd	nd	2.7 ± 1.8	nd	nd	2.8 ± 1.1
IGHA	Ig heavy chain alpha	2.3 ± 0.5	3.0 ± 0.4	2.9 ± 0.9	1.3 ± 0.1	0.7 ± 0.2	3.3 ± 0.7
		2.0 ± 0.3	3.3 ± 0.5	2.4 ± 1.3	1.3 ± 0.1	nd	4.1 ± 1.7
		nd	2.6 ± 0.3	1.7 ± 0.3	1.0 ± 0.0	nd	nd
IGK@**	Ig kappa locus	4.0 ± 0.6	4.1 ± 1.0	2.8 ± 0.6	2.9 ± 0.1	1.3 ± 0.7	3.8 ± 1.7
IGL@	Ig lambda locus	3.6 ± 0.8	4.7 ± 0.8	3.3 ± 1.2	2.1 ± 0.7	1.6 ± 0.7	4.7 ± 1.1
		3.3 ± 0.5	3.6 ± 0.7	3.5 ± 1.6	2.4 ± 0.4	1.1 ± 0.5	6.7 ± 4.5
		nd	0.9 ± 0.3	nd	nd	nd	nd

All probe sets classified as present in at least one of the depots in at least one of the subjects, are listed in the table. Some genes were represented by multiple probe sets on the array. Genes that were not detected in either depot in a subject are shown as nd. Values represent mean ± SD.
*,** The annotation for these probe sets have been changed, previously IGHG3 and IGKC, respectively, as referred to in [11].

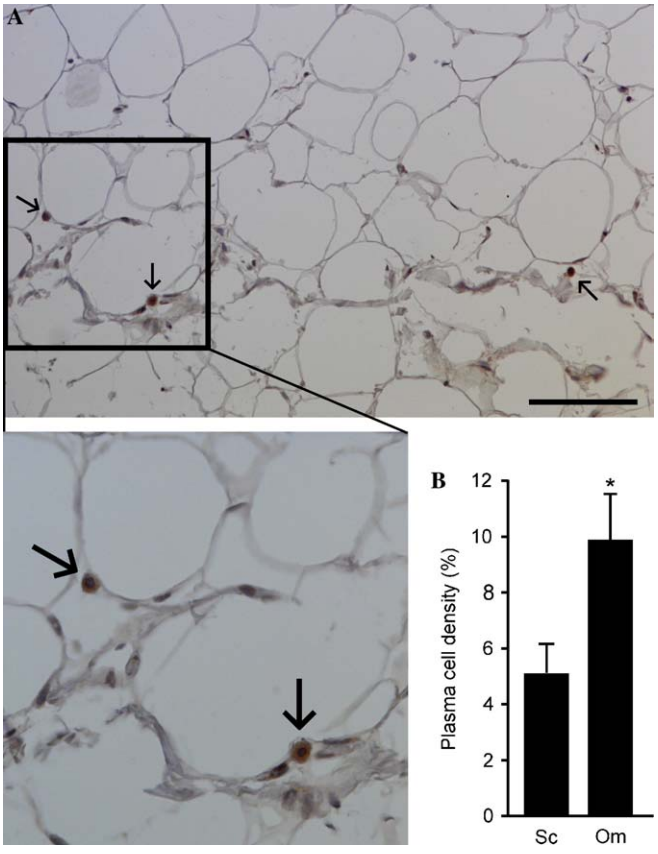

Fig. 1. Plasma cells in human adipose tissue. (A) Representative paraffin section of human omental adipose tissue processed to demonstrate immunoreactivity to plasma cell antigen (dark brown), counterstained by hematoxylin. Arrows indicate plasma cells. Original magnification 20× (upper), 40× (lower), bar = 100 μm. (B) Plasma cell density, expressed as number of plasma cells related to the total number of stroma-vascular nuclei in the same visual fields, in paired biopsies of subcutaneous (sc) and omental (om) adipose tissue (*$p < 0.05$, $n = 20$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.)

FcεR subunit, was absent in all samples. Therefore, FCGRT and FCER1G were not included in further studies. FCGR2A and FCGR2B expression levels were analyzed in a panel of 37 different human tissues and cell types including omental and subcutaneous adipocytes. The FcR expression in 10 of these tissues/cell types is presented in Fig. 2. FCGR2A was highly expressed in adipose tissue and adipocytes from both depots. The corresponding

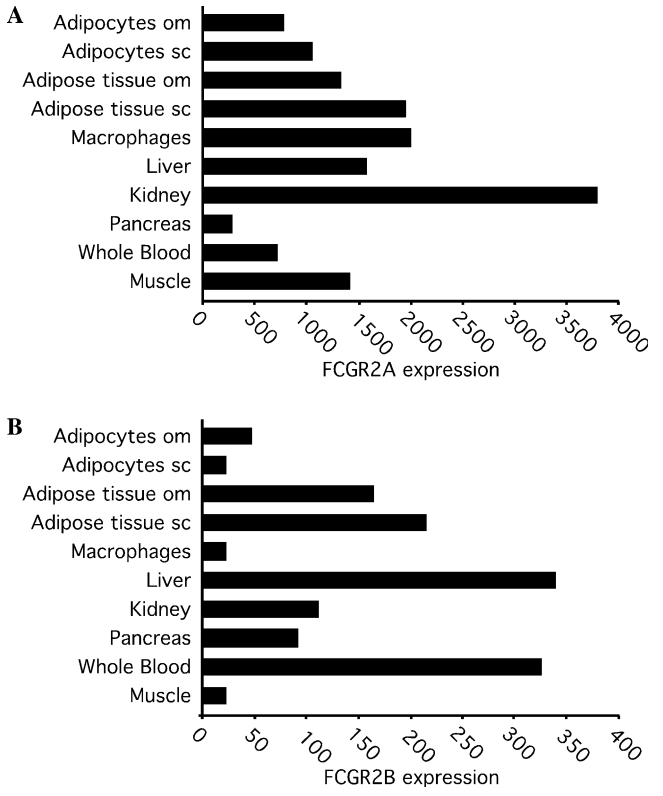

Fig. 2. Expression of (A) FCGR2A and (B) FCGR2B in 10 different human tissues and cell types analyzed by microarray. Omental (om), subcutaneous (sc).

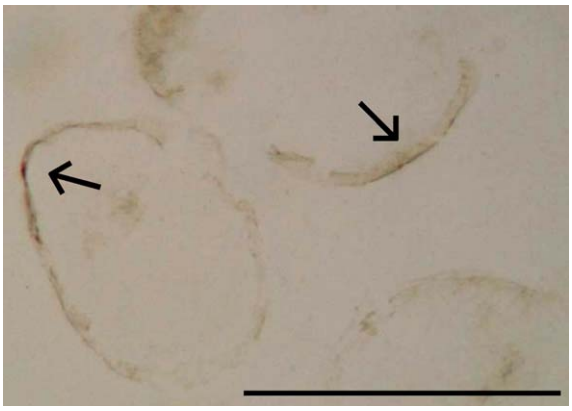

Fig. 3. Cryostat section demonstrating CD32 (FcγRIIa and FcγRIIb) immunoreactivity on omental adipocyte cell membranes. Positive signal appears dark brown (indicated by arrows). Bar = 100 μm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.)

expression of FCGR2B was markedly lower and FCGR2B was classified as absent in subcutaneous adipocytes. FCGR2B showed generally lower expression levels compared to FCRG2A in all tissues and cell types. Using an antibody directed against CD32, which detects both FcγRIIa and FcγRIIb, immunopositive staining was demonstrated on the cell membranes of both subcutaneous and omental adipocytes (Fig. 3).

Effects of Fc on cytokine expression in adipocytes

The effect of Fc on adipocyte cytokine expression was investigated in vitro. Incubations with insulin and TNFα were included for comparison. Fc markedly reduced adipocyte IL-1β and IL-6 expression in all nine incubations ($p < 0.01$), while TNFα expression was not affected. Insulin and TNFα both stimulated adipocyte IL-1β expression ($p < 0.05$). Adipocyte IL-6 expression was stimulated by TNFα ($p < 0.05$) (Fig. 4).

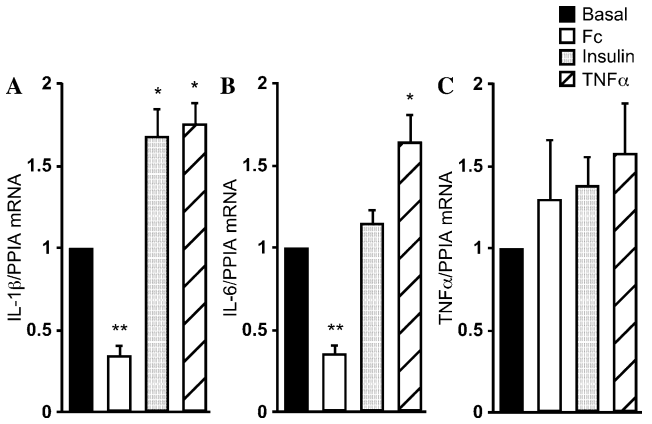

Fig. 4. Real-time RT-PCR analysis of (A) IL-1β, (B) IL-6, and (C) TNFα gene expression in adipocytes after incubation with or without (basal) Fc, insulin or TNFα. Data are normalized to basal levels set to 1.0, $n = 9$ ($^{*}p < 0.05$; $^{**}p < 0.01$).

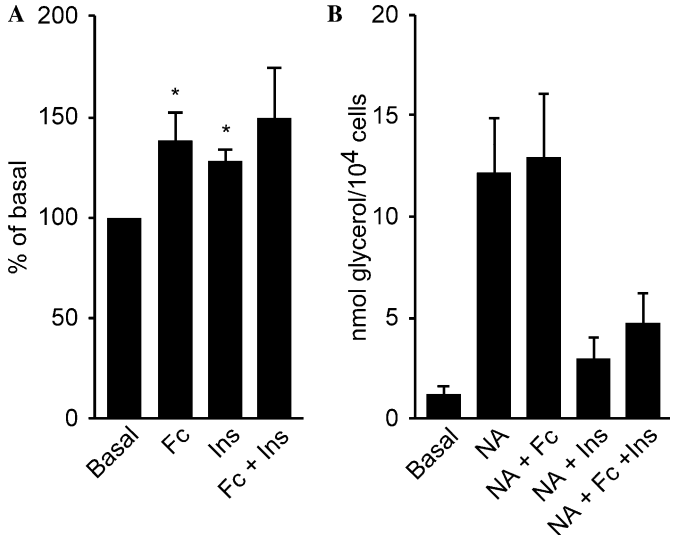

Fig. 5. Effects of Fc on (A) lipogenesis and (B) lipolysis in adipocytes in vitro. Fc fragment of human IgG (Fc), Insulin (Ins), and noradrenaline (NA). (A) Lipogenesis was measured by analyzing glucose incorporation into triglycerides. Adipocytes were incubated with or without (basal), Fc (600 μg/ml), insulin (1000 μU/ml) or Fc/insulin. Lipogenesis at basal condition was set to 100%, $^{*}p < 0.05$, $n = 5$. (B) The glycerol content of the medium was taken as an index of lipolysis. Adipocytes were incubated with or without (basal) noradrenaline (10^{-5} M), noradrenaline/Fc (600 μg/ml), noradrenaline/insulin (1000 μU/ml), and noradrenaline/Fc/insulin, $n = 5$.

Effects of Fc on adipocyte metabolism

The Fc effect on adipocyte metabolism was investigated in vitro. Fc stimulated lipogenesis as potently as insulin ($p < 0.05$). The effect of the combination of Fc and insulin tended, in some incubations, to be additive. However, this effect was not significant due to large variations between incubations (Fig. 5A). Fc influenced neither noradrenaline-induced nor insulin-inhibited lipolysis (Fig. 5B).

Discussion

The present study shows that, in obese subjects, plasma cells are interspersed in adipose tissue. The plasma cell density is about twice as high in the visceral compared to the subcutaneous depot. Moreover, FcR genes are expressed in human adipose tissue and adipocytes from both depots, and the FcγRII is present on the cell membranes of adipocytes. Furthermore, Fc exposure of adipocytes in vitro resulted in markedly reduced expression levels of IL-1β and IL-6 as well as in insulin-like stimulation of lipogenesis. Thus, the current work suggests that Igs produced in adipose tissue by plasma cells exert a paracrine influence on adipocyte function and metabolism via adipocyte FcRs.

The omentum plays a central role in the primary immune defense by rapid absorption and clearance of bacteria and foreign material from the peritoneal cavity [23]. Macrophages, but probably also B lymphocytes, play a critical role in this process. The higher density of plasma cells, i.e., end-point stage of B-cell differentiation, in the

omentum indicates that interactions between the adaptive immune system and the adipocyte are most pronounced in the visceral adipose tissue depot. This idea is also supported by our previous finding of higher expression of Ig genes in omental compared to subcutaneous adipose tissue [11]. It is possible that the depot differences in plasma cell density could be due to differences in plasma cell recruitment by chemokines [24]. However, this could not be evaluated using our microarray data.

FcR mRNA expression in human adipose tissue has not previously been investigated. We found that FCGR2A and FCGRT were highly expressed in adipose tissue and adipocytes in both depots. FCGRT delivers IgGs across the maternofetal barrier during gestation and has also been reported to be responsible for regulating serum IgG levels in mammals [22]. The specific role of FCGRT in adipose tissue remains to be elucidated and due to its divergent function in comparison with the other FcRs it was not included in further studies. In addition to FCGR2A and FCRGT, FCGR2B and FCER1G were also expressed, however, at lower levels and FCGR2B was absent in subcutaneous adipocytes. All genes encoding the FcεR subunits were not expressed in adipocytes, indicating that FcεR is not present on adipocyte membranes. The presence of FcγRII (a and/or b) on adipocyte membranes was verified using immunohistochemistry and our microarray results indicate that this signal is mainly due to FcγRIIa.

The cellular response to the Fc region of IgG depends partly on the relative expression of activating and inhibitory FcγR [25]. FcγRIIa is the most widely expressed activating human FcγR. Most cells of the immune system express this receptor and it has been reported to trigger phagocytosis and release of inflammatory mediators [25]. We found that exposure of adipocytes to Fc resulted in reduced expression of IL-1β and IL-6. This finding suggests that Igs may have an anti-inflammatory effect in human adipose tissue. The biological implication of this observation remains unclear. TNFα stimulates, whereas insulin does not affect IL-6 production in human adipocytes [26,27]. Moreover, TNFα release from human adipocytes in vitro is not influenced by insulin [28]. These observations are consistent with the findings in the present study, suggesting that the cells were responding adequately to treatment.

Interestingly, Fc showed an insulin-like stimulatory effect on lipogenesis in human adipocytes in vitro as previously reported by Khokher et al. [12]. Since IgG has no effect on the specific binding of insulin to its receptors [29], this stimulation of lipogenesis is probably achieved independently of the insulin receptor. Still, cellular activation by FcγRs includes activation of PI3 kinase, required for insulin effects on glucose transport, suggesting that Fc and insulin may influence lipogenesis partly via the same signaling pathway [25,30]. We also studied the effect of Fc on lipolysis, the other major determinant of intracellular triglyceride turnover. Fc influenced neither noradrenaline-induced nor insulin-inhibited lipolysis. Taken together, the results indicate that local production of IgG may favor lipid accumulation and the higher density of plasma cells in omental adipose tissue suggests that the visceral depot may be affected to a greater extent.

In conclusion, our data demonstrate that the prerequisites for paracrine interactions between plasma cells and adipocytes are present in human adipose tissue. Locally produced Igs may stimulate lipogenesis suggesting that Igs are involved in adipose tissue accumulation. In addition, Fc reduces adipocyte IL expression, indicating that Igs have an anti-inflammatory effect in human adipose tissue. The Ig actions described are probably most pronounced in visceral adipose tissue.

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