Regulation of the Fibrosis and Angiogenesis Promoter SPARC/Osteonectin in Human Adipose Tissue by Weight Change, Leptin, Insulin, and Glucose

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OBJECTIVE—Matricellular Secreted Protein, Acidic and Rich in Cysteine (SPARC), originally discovered in bone as osteonectin, is a mediator of collagen deposition and promotes fibrosis. Adipose tissue collagen has recently been found to be linked with metabolic dysregulation. Therefore, we tested the hypothesis that SPARC in human adipose tissue is influenced by glucose metabolism and adipokines.

RESEARCH DESIGN AND METHODS—Serum and adipose tissue biopsies were obtained from morbidly obese nondiabetic subjects undergoing bariatric surgery and lean control subjects for analysis of metabolic markers, SPARC, and various cytokines (RT-PCR). Additionally, 24 obese subjects underwent a very-low-calorie diet of 1,883 kJ (450 kcal)/day for 16 weeks and serial subcutaneous-abdominal-adipose tissue (SCAT) biopsies (weight loss: 28 ± 3.7 kg). Another six lean subjects underwent fast-food–based hyperalimentation for 4 weeks (weight gain: 7.2 ± 1.6 kg). Finally, visceral adipose tissue explants were cultured with recombinant leptin, insulin, and glucose, and SPARC mRNA and protein expression determined by Western blot analyses.

RESULTS—SPARC expression in human adipose tissue correlated with fat mass and was higher in SCAT. Weight loss induced by very-low-calorie diet lowered SPARC expression by 33% and increased by 30% in adipose tissue of subjects gaining weight after a fast-food diet. SPARC expression was correlated with leptin independent of fat mass and correlated with homeostasis model assessment–insulin resistance. In vitro experiments showed that leptin and insulin potently increased SPARC production dose dependently in visceral adipose tissue explants, while glucose decreased SPARC protein.

CONCLUSIONS—Our data suggest that SPARC expression is predominant in subcutaneous fat and its expression and secretion in adipose tissue are influenced by fat mass, leptin, insulin, and glucose. The profibrotic effects of SPARC may contribute to metabolic dysregulation in obesity. Diabetes 58:1780–1788, 2009

Secreted Protein, Acidic and Rich in Cysteine (SPARC), a 34-kDa matricellular glycoprotein, is also known as osteonectin and BM-40. It was initially found to be secreted from bone (1), but SPARC is expressed in most tissues and was the first extracellular matrix protein described in adipose tissue (2,3).

SPARC is a multifunctional protein: it is involved in osteogenesis, angiogenesis, wound healing, tumorigenesis, and the pathogenesis of fibrosis involving the kidney (4,5) and liver (6). SPARC also contributes to collagen fibril formation in the dermis, and SPARC knockout mice have reduced collagen content in the dermis (7). More recent evidence suggests that fibrosis in adipose tissue impairs metabolic function and reduces the capacity of fat expansion (3). SPARC is secreted from human adipose tissue and is predominantly derived from adipocytes, where it has a role in adipocyte differentiation, adipogenesis, and adipose tissue hyperplasia (2,8); however, it is unknown whether SPARC contributes to the pathogenesis of insulin resistance or the metabolic syndrome. The aim of this study was therefore to study 1) the depot-specific expression of SPARC, 2) the association of SPARC with markers of insulin resistance, 3) the association of SPARC adipose tissue expression with the adipokines leptin and adiponectin, and 4) the effect of weight loss and weight gain on adipose tissue SPARC expression.

We determined the adipose tissue depot expression in visceral fat (VAT) and subcutaneous abdominal adipose tissue (SCAT) in lean and morbidly obese subjects in association with adipokine levels and markers of insulin resistance and explored the gene expression of SPARC in a longitudinal intervention study involving obese subjects treated with a very-low-calorie diet (VLCD) to induce weight loss. Cell culture studies confirmed the regulation of SPARC by insulin, glucose, and leptin.

RESEARCH DESIGN AND METHODS
Subjects for adipose tissue depot study. Volunteers were recruited from adults undergoing bariatric surgery (obese group) and routine abdominal surgery (lean group) at the University Hospital Aintree, Liverpool, after ethical permission from the local research ethics committee. Subjects with diabetes, inflammatory disorders, or infectious or malignant diseases and subjects on drug treatments that would likely affect body weight or any study variables, including endocrine diseases and treatments with systemic glucocorticoids, were excluded. Lean and obese participants were of similar age and had the following patient characteristics: obese group—13 men and 26 women, age 44.5 ± 1.4 years (mean ± SD), BMI 46.8 ± 1.9 kg/m², n = 39; lean group—10 men and 8 women, age 42.3 ± 4.1 years, BMI 23.6 ± 0.8 kg/m², n = 18. Volunteers attended the clinical investigation unit after an overnight fast from...
TABLE 1  
Subject characteristics from Aintree study population

| Characteristic                  | Lean     | Obese    | Significance | P value |
|---------------------------------|----------|----------|--------------|---------|
| Sex (male/female)               | 10/8     | 13/26    | NS           |         |
| Age (years)                     | 42.3 ± 17.3 | 44.6 ± 9 | NS           |         |
| BMI (kg/m²)                     | 23.6 ± 2.1 | 46.9 ± 11.7 | <0.001     |         |
| Waist (cm)                      | 88.6 ± 12 | 130 ± 28 | <0.001      |         |
| Systolic blood pressure (mmHg)  | 129 ± 13 | 143 ± 19 | <0.01       |         |
| Diastolic blood pressure (mmHg) | 76 ± 9   | 88 ± 14  | <0.01       |         |
| HOMA-IR                         | 1.8 ± 0.3 | 4.3 ± 0.6 | <0.001      |         |
| C-reactive protein (ng/ml)      | 1.55 ± 1 | 11.9 ± 5.7 | <0.001    |         |

Characteristics of lean and obese subjects recruited for biopsies of SCAT and VAT. Subjects differ in metabolic variables including blood pressure and HOMA-IR. n = 56.

TABLE 2  
VLCD study patient characteristics

| Characteristic                  | Baseline | 8 weeks | 16 weeks | 18 weeks |
|---------------------------------|----------|---------|----------|----------|
| Weight (kg)                     | 119 ± 20 | 101 ± 17 | 91 ± 16 | 91 ± 16*** |
| BMI (kg/m²)                     | 37.6 ± 4.9 | 31.8 ± 4.1 | 28.6 ± 4.1 | 28.9 ± 3.9*** |
| Waist (cm)                      | 123 ± 12 | 110 ± 12 | 101 ± 13 | 101 ± 13*** |
| Waist-to-hip ratio              | 1.0 ± 0.08 | 0.99 ± 0.08 | 0.95 ± 0.08 | 0.95 ± 0.08*** |
| Fasting glucose (mmol/L)        | 6.0 ± 1.6 | 4.5 ± 0.7 | 4.5 ± 0.7 | 5.0 ± 1.0*** |
| OGTT 2-h glucose (mmol/L)       | 8.2 ± 3.8 | 7.0 ± 1.9 | 7.0 ± 2.6 | 5.9 ± 2.3*** |
| Fasting insulin (mU/L)          | 16 ± 7.4 | 7.0 ± 4.1 | 4.3 ± 2.2 | 6.3 ± 3.7*** |
| HOMA-IR                         | 4.4 ± 2.7 | 1.4 ± 0.9 | 0.9 ± 0.5 | 1.5 ± 1.3*** |
| Total abdominal fat area (cm²)  | 778 ± 191 | —      | 416 ± 171** | — |
| SCAT area (cm²)                 | 526 ± 166 | —      | 308 ± 135** | — |
| VAT area (cm²)                  | 241 ± 76 | —      | 101 ± 48** | — |
| Systolic blood pressure (mmHg)  | 138 ± 17 | 121 ± 12 | 117 ± 14 | 124 ± 16*** |
| Total cholesterol               | 5.7 ± 1.1 | 3.9 ± 0.9 | 4.4 ± 0.8 | 4.9 ± 0.8*** |
| Serum leptin                    | 38.8 ± 19 | 9.8 ± 7.5 | 6.5 ± 5.9 | 8.8 ± 6.7*** |
| Serum adiponectin               | 9.0 ± 5.3 | 11.5 ± 7.3 | 13.6 ± 6.4 | 15.2 ± 7.9*** |
| C-reactive protein (mg/l)       | 5.3 ± 5.8 | 4.6 ± 5.4 | 2.4 ± 1.5 | 2.4 ± 2.2*** |
| SPARC (signal units)            | 1,857 ± 66 | 1,186 ± 82*** | 1,087 ± 80*** | 1,217 ± 82*** |

Data are means ± SD. A computed tomography was performed at weeks 0 and 16 for adipose tissue area calculations. SCAT biopsy samples were obtained with a syringe with manually applied vacuum under local anesthesia and immediately frozen in liquid nitrogen and stored at −80°C until analysis. Microarray analysis of SCAT biopsies was performed on 24 patients of which 12 subjects (three women and nine men) were obese but healthy and 12 subjects (three women and nine men) were dysmetabolic according to the above criteria. Patient characteristics are shown in Table 2. Biochemical and anthropometrical measurements and examinations were performed as described (9). Computed tomography was used to determine body composition as previously described (11).

**VLCD study.** Subjects for the VLCD study that aims to identify gene expression changes in adipose tissue of obese subjects undergoing weight loss from caloric restriction were recruited for a 6 month VLCD treatment (week 18). Anthropometrical measurements, blood pressure, weight, and height were recorded by the same observer, and BMI was calculated. Waist circumferences were recorded by measurement at the midpoint between iliac crest and lowest point of the costal margin. Body composition was estimated by electrical bio-impedance measurement using a four-pole system. Blood sampling, oral glucose tolerance test, and a SCAT biopsy were performed at each of the four time points. Computed tomography performed at weeks 0 and 16 was used for adipose tissue area calculations. SCAT biopsy samples were obtained with a syringe with manually applied vacuum under local anesthesia and immediately frozen in liquid nitrogen and stored at −80°C until analysis. Microarray analysis of SCAT biopsies was performed on 24 patients of which 12 subjects (three women and nine men) were obese but healthy and 12 subjects (three women and nine men) were dysmetabolic according to the above criteria. Patient characteristics are shown in Table 2. Biochemical and anthropometrical measurements and examinations were performed as described (9). Computed tomography was used to determine body composition as previously described (11).
SPARC’s metabolic regulation in human adipose tissue

TABLE 3
Hyperalimentation study

| Sex (male/female) | Age (years) | Weight (kg) | BMI (kg/m²) | Fat mass (kg) | Systolic blood pressure (mmHg) | Fasting glucose (mmol/L) | Fasting Insulin (mU/L) | HOMA-IR | C-reactive protein (ng/ml) | Serum leptin (ng/ml) | SPARC (signal units) |
|------------------|-------------|-------------|-------------|--------------|-------------------------------|-------------------------|-----------------------|---------|---------------------------|-------------------|---------------------|
| 4/2              | 24 ± 3      | 64.2 ± 9.3  | 21.4 ± 2.5  | 11.6 ± 6.6   | 115 ± 8                      | 5.15 ± 0.72             | 4.2 ± 2.7             | 0.7 ± 0.5 | 0.28                      | 6.4 ± 10.9        | 3.5 ± 0.8           |

Baseline | Week 4 | Significance | P value |
|---------|--------|--------------|---------|

Note: Data are presented as mean ± SD. NS, not significant.

Microarray analysis. For microarray analysis, samples were pooled for each patient (n = 6) and arrayed across three Affymetrix HG U133A microarrays (Affymetrix, Santa Clara, CA). Gene expression was measured using Affymetrix HG U133A microarrays. All Affymetrix expression values were log2 transformed.

RESULTS

SPARC expression in adipose tissue and its depots.

Our data showed that SPARC was expressed in various human tissues but especially in adipocytes where the expression was higher in larger cells (Fig. 1A). The expression in adipocytes was greater than the expression in stroma cells of adipose tissue (data not shown). When comparing adipose tissue depot expression, SPARC expression was higher in SCAT than VAT (0.81 ± 0.06 vs. 0.50 ± 0.03 signal units, P < 0.001, n = 47, Fig. 1B) similar to the expression of the adipokine leptin in SCAT (1.53 ± 0.1 vs. 0.6 ± 0.03 signal units, P < 0.001, n = 47, Fig. 1A).

SPARC and indicators of obesity and obesity-related inflammation. We did not find a sex difference in expression of BMI-matched men and women. Both SCAT- and VAT-derived SPARC showed a positive correlation with fat mass (Fig. 2) and with waist circumference (Table 4) in the depot study. SPARC was strongly correlated with high-sensitivity C-reactive protein but not with circulating tumor necrosis factor-α (TNF-α) or interleukin-6 (IL-6). SPARC was correlated with local adipose tissue expression.
of the macrophage-migration inhibitory factor (MMIF; \( r = 0.3, \ P < 0.05 \)), but only SCAT expression of SPARC correlated with local IL-6 expression (\( r = -0.3, \ P < 0.05 \)). TNF-\( \alpha \), macrophage inflammatory protein-1 (MIP-1), monocyte chemoattractant protein-1 (MCP-1), or regulated upon activation normal T-cell expressed and secreted expression showed no association with SPARC expression (Table 4).

**SPARC and markers of insulin resistance.** SPARC was associated with fasting insulin levels (SCAT: \( r = 0.31, \ P = 0.04 \); VAT: \( r = 0.34, \ P = 0.02 \)) and homeostasis model assessment–insulin resistance (HOMA-IR; SCAT: \( r = 0.32, \ P = 0.03 \); VAT: \( r = 0.36, \ P = 0.016 \)). In addition, VAT-SPARC expression but not SCAT-SPARC was correlated with fasting glucose (\( r = 0.29, \ P = 0.046 \), Table 4).

**SPARC and the adipokines leptin and adiponectin.** VAT-SPARC correlated with VAT leptin (\( r = 0.55, \ P < 0.001 \)) and SCAT-SPARC with SCAT leptin (\( r = 0.68, \ P < 0.001 \)); this remained significant after correction for fat mass, waist-to-hip ratio, and HOMA-IR. VAT-SPARC was negatively correlated with serum adiponectin (\( r = -0.37, \ P < 0.01 \)) and SCAT-SPARC but not VAT-SPARC negatively correlated with SCAT adiponectin (\( r = -0.3, \ P < 0.05 \); Fig. 2C, Table 4).

**SPARC and weight loss.** Obese subjects in the VLCD study lost 18 kg in the first 8 weeks and an additional 10 kg by week 16. There was no further weight loss from week 16 to 18. The average SPARC expression in the adipose tissue of these subjects decreased by 33\% in the first 8 weeks (\( P < 0.0001, \ paired \ t \ test \)). However, despite further weight loss, there was no change in SPARC expression between 8 and 16 weeks (\( P = 0.74, \ paired \ t \ test \)). Between 16 and 18 weeks, during which period the subjects went from VLCD to regular food while remaining weight stable, the SPARC expression increased significantly (20\% rise, \( P < 0.0001, \ paired \ t \ test \)) and remained significantly correlated with insulin, glucose, and leptin levels but not adiponectin levels (data not shown). There was no difference in SCAT-SPARC expression in the group with the metabolic syndrome, but there was a tendency to a further decline of SPARC at week 16 (Fig. 3).

**SPARC regulation by insulin and glucose.** Cell culture studies were performed to determine whether the observed correlations of SPARC with metabolic parameters are because of direct regulation by glucose, leptin, or insulin. Increasing doses of glucose (5, 10, 20, and 40 mmol/l) decreased SPARC protein expression (5 mmol/l: 100 ± 8 optical density units; 10 mmol/l: 93 ± 6 optical density units; 20 mmol/l: 24 ± 6 optical density units; 40 mmol/l: 19 ± 4 optical density units [SPARC/β-actin], respectively, \( n = 6; \ P < 0.01 \), Fig. 4A). In contrast, culture of VAT with insulin (0, 0.01, 1, and 100 nmol/l) increased SPARC expression (C: 100 ± 20 optical density units; 0.01 nmol/l: 105 ± 35 optical density units; 1 nmol/l: 156 ± 27 optical density units; 100 nmol/l: 292 ± 30 optical density units, \( n = 6; \ P < 0.001 \); Fig. 4B).

**SPARC regulation by leptin.** Similar to insulin, leptin treatment of visceral fat explants showed a dose-
dependent increment of SPARC expression (C: 100 ± 20 optical density units; 0.1 nmol/l: 271 ± 30 optical density units; 10 nmol/l: 465 ± 52 optical density units; P < 0.001; Fig. 4C).

**DISCUSSION**

Adipose tissue plays a key role in energy homeostasis both as an energy store and as an endocrine organ. Dysfunction of adipose tissue fat storage leads to fat deposition in other organs as ectopic fat and results in disadvantageous metabolic consequences as most apparent in subjects with familial lipodystrophy (19). The cause of impaired adipose tissue storage capacity is unclear and SPARC that influences matricellular composition could contribute to its development by inhibition of adipocyte differentiation. Disturbance of the 3D extracellular matrix (ECM), for example, increased rigidity by increased collagen 1 content and has previously been shown to compromise in vitro adipocyte differentiation (20), and collagen dysregulation has recently been attributed to metabolic dysregulation (3).

The following attributes make SPARC a likely candidate to limit fat deposition in adipose tissue itself. Although it is an evolutionarily conserved collagen-binding glycoprotein, it does not contribute to the structure of the ECM, but it was recently shown to be a ligand of the integrin receptor α5β1-integrin (21) and inhibit adipogenesis through stimulation of β-catenin signaling (8), which is part of the Wnt pathway that enhances osteoblastogenesis alongside the inhibition of adipogenesis (22). SPARC null mice have a phenotype marked by an increased subcutaneous fat deposition, reduction in collagen 1 in SPARC-null fat, adipocytes of higher diameters, and fat pads with an increase in adipocyte number (23).

The results of our study showed an increase of SPARC expression with increased fat mass that is consistent with previous reports showing a higher expression of SPARC in rodent obesity (24) and elevated SPARC levels in obese subjects (25). In addition, this is the first study to highlight the depot-specific expression of SPARC in humans. SPARC/osteonectin is expressed in various human tissues with particularly high expression in subcutaneous abdominal fat where is appears to be secreted primarily by adipocytes in comparison to the adipose tissue stromal fraction that is consistent with previous findings (2).

Subjects with familial lipodystrophy lack SCAT, and the metabolic consequences could be attributed to the limitation of subcutaneous tissue expansion to which SPARC as an inhibitor of adipogenesis (8) with higher expression in SCAT may contribute.

This is the first study to assess metabolic parameters in combination with adipose tissue SPARC expression. We found a positive correlation with fasting insulin, fasting glucose, and HOMA-IR and waist circumference as well as hsCRP for subcutaneous and visceral depot. However, we did not find a correlation of SPARC with fasting lipids or blood pressure, which may in part be masked by treatment

**FIG. 2.** SPARC and relation to fat mass, HOMA-IR, and adipokine expression. A: Depot expression of SPARC and its correlation with fat mass. B: VAT and SCAT-SPARC expression and HOMA-IR. C: VAT expression of adiponectin and SPARC. D: The correlation of SPARC expression with leptin. Values are expressed in signal units.
of subjects with hypercholesterolemia and hypertension (not shown).

Higami et al. (26) examined genes downregulated by energy restriction in epididymal fat in mice, and SPARC was one of the prominently affected genes lowered by long-term energy restriction. Consistent with this we have found a strong downregulation of SPARC with weight loss after 8 weeks of a VLCD and an increment of SPARC with weight gain. Although HOMA-IR improved with weight loss in our VLCD study population, and SCAT-SPARC expression correlated with fasting insulin and HOMA-IR, the SPARC expression was no different in the BMI-matched groups with and without the metabolic syndrome, which is explained and consistent with the lack of correlation of SPARC with blood pressure and lipids. Leptin is a strong predictor of SPARC in the depot study as well as the VLCD study in which it is independent of the BMI at baseline. SPARC remains correlated with leptin expression but loses its association with weight loss after 8 weeks, after which subjects continued to lose weight. The strong correlation with insulin, glucose, and leptin in the depot and the VLCD study prompted us to study and confirm their regulation by further in vitro studies, while adiponectin showed an inverse correlation with SPARC expression in SCAT but not VAT and thus appeared less likely to be because of a direct effect.

Culture of visceral explants showed that glucose lowered and insulin and leptin increased SPARC expression that apart from the glucose correlation is consistent with the findings in the clinical studies. However, circulating glucose in vivo showed a positive correlation with SPARC-AT expression that contradicts the in vitro study in which supraphysiological glucose levels lower SPARC. The lack of influence of circulating glucose levels may be explained by the insulin resistance of adipocytes for glucose transport in obese individuals. In diabetic subjects, we would expect the glucose levels required to lower SPARC to be supraphysiological as found in marked hyperglycemia that is usually avoided by antidiabetic treatment. Although we show that SPARC is regulated by leptin, SPARC in turn suppresses leptin gene expression in mouse preadipocytes (21), which may explain the high leptin levels observed in SPARC knockout mice (23). It was suggested that SPARC may be involved in inflammatory processes (27,28), but data from our study show only a correlation of adipose tissue SPARC expression with the local expression of the MMIF-1—a proinflammatory adipocytokine (29). An association of SPARC with MMIF was to our knowledge only reported in connection.
FIG. 3. SPARC during VLCD 16-week 450 kcal/day in subjects with (METS+) and without (METS−) the metabolic syndrome. Data from SPARC adipose tissue expression of subjects of both groups were compared with their baseline levels (top) and the within-patient variation with the previous time point. R, refeeding; W, week. **p < 0.01, ***p < 0.001, n = 24.

TABLE 4
SPARC and metabolic parameters and cytokines

|                          | SCAT        | VAT          |
|--------------------------|-------------|--------------|
| Waist circumference (cm) | R = 0.37, p < 0.01 | R = 0.23, p < 0.05 |
| Fat mass (kg)            | R = 0.4, p < 0.01 | R = 0.3, p < 0.05 |
| Total cholesterol (mmol/l)| R = 0.008, p = NS | R = 0.23, p < 0.05 |
| Fasting insulin (μIU/ml) | R = 0.31, p < 0.05 | R = 0.34, p < 0.05 |
| Fasting glucose (mmol/l) | R = 0.23, p = NS | R = 0.3, p < 0.05 |
| HOMA-IR                  | R = 0.32, p < 0.05 | R = 0.36, p < 0.05 |
| Circulating leptin (ng/ml)| R = 0.17, p = NS | R = 0.17, p = NS |
| Circulating adiponectin (ng/ml)| R = 0.22, p = NS | R = 0.37, p < 0.05 |
| Circulating IL-6 (ng/ml)  | R = 0.26, p = NS | R = 0.01, p = NS |
| Circulating TNF-α (ng/ml) | R = 0.16, p = NS | R = 0.03, p = NS |
| hsCRP (mmol/l)           | R = 0.44, p < 0.01 | R = 0.31, p < 0.05 |
| Adipose tissue leptin    | R = 0.68, p < 0.001 | R = 0.55, p < 0.001 |
| Adipose tissue adiponectin| R = 0.3, p < 0.05 | R = 0.1, p = NS |
| Adipose tissue IL-6      | R = 0.34, p = 0.05 | R = 0.1, p = NS |
| Adipose tissue MMIF      | R = 0.07, p = NS | R = 0.03, p = NS |
| Adipose tissue TNF-α     | R = 0.07, p = NS | R = 0.03, p = NS |
| Adipose tissue MIP-1     | R = 0.03, p = NS | R = 0.47, p = NS |
| Adipose tissue MCP-1     | R = 0.055, p = NS | R = 0.14, p = NS |
| Adipose tissue RANTES    | R = 0.077, p = NS | R = 0.017, p = NS |

SPARC depot-specific expression in relation to metabolic parameters, circulating cytokine levels, and adipose tissue expression of adipokine/cytokine corresponding to the depot studied. RANTES, regulated upon activation normal T-cell expressed and secreted. n = 56, significant correlations are shown in bold.

with malignant melanoma cells that showed overexpression of both (30). Thus, the interaction of SPARC and MMIF remains to be confirmed but may explain a potential association of SPARC with diabetes with MMIF being associated with the pathogenesis of type 1 and type 2 diabetes and latter among others through a decrease in insulin signal transduction (31).

Much pathology related to diabetes and obesity has been linked with SPARC. An increased SPARC expression was found in rodent models of diabetic nephropathy (32), and SPARC null mice were shown to be protected from renal fibrosis (27). Increased circulating levels of SPARC have been observed in subjects with cardiovascular disease (25). SPARC is also expressed in human retinal endothelial cells (33), and with its close interaction with VEGF and PAI-1 (34,35) it may further the progression of diabetic retinopathy. Furthermore, SPARC is linked with tumorigenesis and appears to favor certain tumors (36), although its exact role in tumor development is controversial (37) and it remains to be shown whether SPARC could contribute to the association of obesity and some cancers (38).

Apart from focusing on the potential advantages of lowering SPARC levels, the inducers of SPARC excess both (30). Thus, the interaction of SPARC and MMIF remains to be confirmed but may explain a potential association of SPARC with diabetes with MMIF being associated with the pathogenesis of type 1 and type 2 diabetes and latter among others through a decrease in insulin signal transduction (31).

Much pathology related to diabetes and obesity has been linked with SPARC. An increased SPARC expression was found in rodent models of diabetic nephropathy (32), and SPARC null mice were shown to be protected from renal fibrosis (27). Increased circulating levels of SPARC have been observed in subjects with cardiovascular disease (25). SPARC is also expressed in human retinal endothelial cells (33), and with its close interaction with VEGF and PAI-1 (34,35) it may further the progression of diabetic retinopathy. Furthermore, SPARC is linked with tumorigenesis and appears to favor certain tumors (36), although its exact role in tumor development is controversial (37) and it remains to be shown whether SPARC could contribute to the association of obesity and some cancers (38).

Apart from focusing on the potential advantages of lowering SPARC levels, the inducers of SPARC excess such as hyperleptinemia in subjects with leptin resistance and hyperinsulinemia in type 2 diabetes require similar
response to chronic toxic liver injury (39). As such, hyperleptinemia in adipose tissue may through upregulation of SPARC also induce adipose tissue fibrosis that requires further study.

In summary, our study showed that SPARC AT expression is related to human metabolism and SPARC expression that is predominant in SCAT is upregulated by insulin and leptin. Together with the previous reported consequences of SPARC in other tissues, a role for SPARC in the development of obesity- and diabetes-related complications is likely. Further research is required to show whether increased adipose tissue SPARC limits the expansion of normal adipose tissue in response to energy excess and promotes ectopic fat deposition and associated metabolic dysfunction.

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FIG. 4. A: Dose-dependent effects of d-glucose on SPARC protein production in VAT explants assessed by Western blotting. Densitometric analysis of SPARC immune complexes (35 kDa) were normalized to β-actin (40 kDa). Data are expressed as percentage difference of median of basal. B: Dose-dependent effects of insulin on SPARC protein production. C: Dose-dependent effects of leptin on SPARC production. *P < 0.05, **P < 0.01, ***P < 0.001, n = 6.

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