Identification of omentin as a novel depot-specific adipokine in human adipose tissue: possible role in modulating insulin action

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RESEARCH DESIGN AND METHODS

EST sequencing and cloning of omentin cDNA. An adipose λTriplEx cDNA library was purchased from Clontech (cat. no. HL50286), which
was made from a pool of om fat of 11 individuals who succumbed to sudden death. This phage library was converted to a plasmid library by transduction according to the manufacturer’s specifications. The bacterial colonies were randomly picked and dissolved individually in 100 μl of 1× Expand PCR Buffer 2 (Boehringer Mannheim, Indianapolis, IN). Twenty microcolonies of the colony suspension were used as a template for cDNA insert amplification by long PCR with two insert-flanking vector primers (forward: 5'-CTCAGGAAAGCCGCACTTGTGTTG-3’; reverse: 5'-AATACGACTCACTATAGGGGAATTCG-3’). The PCR conditions were 94°C for 2 min followed by 10 cycles of 94°C for 20 s, 58°C for 30 s, and 68°C for 4 min, then by 20 cycles of 94°C for 20 s, 58°C for 30 s, and 68°C for 4 min plus 5-s intervals with each successive cycle, with final extension at 72°C for 7 min. An aliquot of each PCR product was electrophoresed on a 1% agarose gel, and another aliquot was purified with a PCR purification kit (Edge Systems, Gaithersburg, MD) and sequenced with a nested 5’-primer, 5’-GTGGTACCCGGAAATTC-3’, using Big Dye reagents (Applied Biosystems, Foster City, CA).

Expression and purification of omentin. The EST clone p6283 (Genbank acc. no. CB266342 ) is a full-length omentin cDNA and served as the template for PCR amplification of omentin sequence. For omentin expression, the following plasmids were constructed: 1) For antibody production, a cDNA encoding amino acid residues 72–313 of omentin was amplified with forward primer 5’-ACCTCTTGTCAATAGCCTTGCGGGTGCCGC-3’ and reverse primer 5’-CCTCCCCAACAAGCTTTCAACGATAGAAGAC-3’, using the high-fidelity PCR system (Boehringer Mannheim), and subcloned into vector PET28 (Novagen) to create the plasmid p6329, which was verified by sequencing and transformed into Escherichia coli Tuner (Novagen). The His(6)-tagged protein was overexpressed by isopropylthigalactoside induction (40) and purified with Ni2+-NTA resin (Qiagen) under denaturing conditions (8 M urea) to remove cell debris and other contaminants. 2) For the in vitro secretion studies, we tagged the Flag peptide sequence to the coding region of omentin (omentin-F) at the carboxy terminus by PCR with primers 5’-GAGAAGCTTAGTCGTCGTCCTTGTAATC-3’ and 5’-GCAAATGTGGATCCACAATGAACCAACTCAGCTTC-3’, which was verified by sequencing and transformed into Escherichia coli Tuner (Novagen). The protein was eluted with a buffer containing 2 M urea, 0.5 M Tris–HCl, pH 8, and reverse transcription was carried out in the reaction containing 1 μg of total RNA, poly(dT) primer, and Moloney murine leukemia virus reverse transcriptase using the Advantage kit (Clontech). Quantitative real-time PCR (qRT-PCR) of omentin was conducted on an ABI PRISM 7900 Sequence Detection System (ABI, Foster City, CA) using a TaqMan PCR kit and Gene Expression Assay primer and probe set (assay ID: Hs00121437_m1). Cyclophilin A (Assay ID: Hs99999904_m1) mRNA was used as an internal control for normalization of cDNA loading. Threshold cycle (CT) values were obtained and relative gene expression was calculated using the formula 2^{-ΔΔCT} with sc fat cell fraction as reference.

Western analysis. Reduced cell lysates or immunoprecipitates were separated by electrophoresis on 4–20% polyacrylamide gels (Gradi-pore, Hawthorne, NY). After electrophoresis, proteins were transferred onto polyvinylidene difluoride membranes, and bound proteins were probed with primary omentin antibody. Immunodetection was achieved by enhanced chemiluminescence (ECL; Pierce). For the fat explant study, human adipose tissue biopsies (om and sc) were minced and cultured in M 199 medium (0.4 g tissue fragments/15 ml). The cultured media during the first 48-h period were collected and concentrated 30 times by ultrafiltration through Centricon-10 filters (Millipore) before being subject to Western blot analysis with monoclonal anti-omentin antibody 3G1B3 (110 μg/ml). For detection of circulating omentin in blood, 5 ml of human plasma were incubated with 20 μl of polyclonal omentin antiserum or preimmune serum (control) and protein A-Sepharose beads at 4°C for 4 h. The beads were precipitated, washed, and subjected to immunoblotting with polyclonal anti-omentin antiserum (1:1,000 dilution).

Immunofluorescence microscopy. Human adipose tissue cryosectioned (20 μM sections), fixed with 3% paraformaldehyde, and permeabilized with 0.5% cold Triton X-100. The tissue slides were then incubated with polyclonal anti-omentin or preimmune IgG (2.5 mg/ml PBS) at 1:1,000 dilution, washed, and reincubated with a second antibody (goat anti-rabbit IgG-Alexa 568; Molecular Probes). The slides were counterstained with 4,6-diamidino-2-phenylindole to reveal nuclei.

Glucose transport assay and Akt phosphorylation. Human om and abdominal sc adipose biopsies were obtained from healthy individuals undergoing elective or semielective surgery at the University of Maryland Medical Center after written informed consent was obtained, or were purchased from the National Disease Research Interchange (Philadelphia, PA). All other human RNAs were purchased from Clontech. For Northern analysis, adipose total RNAs were prepared with TRIzol (Life Technologies) from human and rhesus monkey freshly frozen om and sc abdominal fat tissues. For murine Northern analysis, male C57BL/6J mice (Jackson Laboratory) aged 7–9 wk were euthanized by CO2, and the tissues of interest were excised and snap-frozen in liquid nitrogen. Total RNA was extracted with TRIzol. Fifteen micrograms of total RNA were loaded per lane for Northern analysis. The human omentin cDNA probe corresponded to nucleotides 263–1,270 of AY549722 and human leptin cDNA to nucleotides 29–1,418 of XM_004625 in GenBank. The murine cDNA omentin probe corresponded to 771–1,018 of in 174904696, whose human homolog is identical to human omentin. All probes were randomly labeled (Stratagene) with [32P]dCTP, hybridization was carried out at 65°C in Rapid-hyb buffer (Amersham), and blots were washed twice with 0.5× SSC-1% SDS at 65°C (stringent wash).
Maryland Medical Center. Alternatively, sc abdominal adipose tissue was obtained by needle aspiration under local anesthesia from healthy subjects (BMI 25.4 to 66.9 kg/m², 35 to 72 yr of age). The glucose transport assay was conducted according to Kashwagi et al. (22), as previously described (19). Briefly, human adipocytes were isolated from sc abdominal fat tissue by collagenase digestion and centrifugation in the presence of 200 nM adenosine. The cells were preincubated at 37°C with omentin at the indicated concentrations or vehicle for 60 min followed by incubation with insulin (3 nM) or vehicle for an additional 15 min. A trace amount (300 nM) of [3-14C]glucose (0.1 μCi/ml) was then added, and the incubation was continued for 1 h at 37°C (12, 19). The radioactivity associated with the fat cell layer was separated and quantitated by a liquid scintillation analyzer (Beckman Coulter) and normalized by fat cell lipid content. Glucose transport was expressed as glucose clearance (fl·cell⁻¹·s⁻¹) (19, 22). For Akt1 phosphorylation, the isolated adipocytes were incubated with omentin (300 ng/ml) for various time intervals and then treated with or without insulin at indicated concentrations for 5 min. The reaction was stopped by separating adipocytes from media by centrifugation through silicone oil. The cells were dissolved in lysis buffer containing 50 mM HEPES, 150 mM sodium chloride, 1 mM EDTA, 1% NP-40, and protease inhibitor cocktail. After centrifugation, the infranatents were subjected to immunoblotting analysis with a mixture of two phospho-specific antibodies against Ser473- and Thr108-phosphorylated Akt1 (Cell Signaling Technology, Beverly, MA) or with general Akt1 antibody (Cell Signaling Technology) to measure total Akt1 in the lysates.

Statistical analysis. Results are expressed as means ± SE. Data were analyzed by two-way repeated-measures ANOVA of the log-transformed data. When main effects of insulin, omentin, or the interaction were statistically significant, a post hoc Bonferroni paired t-test was used to test differences between means. Differences were considered to be significant at P < 0.05.

RESULTS

Identification of omentin cDNA. To identify genes preferentially or specifically expressed in the om fat depot, we conducted systematic EST sequencing of an unnormalized and directional cDNA library made from human om adipose tissue. We developed a protocol that enabled us to directly amplify the cDNA inserts by PCR from bacterial colonies plated from the library (see Research Design and Methods). We performed about 15,300 DNA sequencing reactions of the 5’ ends of PCR products and obtained 10,437 analyzable ESTs, which were subjected to bioinformatics analysis. One cluster of ESTs stood out for its abundance and novelty. This gene cluster contained 39 ESTs, many more than other adipose abundant genes, such as perilipin (12 ESTs), adiponectin (7 ESTs), and leptin (1 EST). Furthermore, it had no significant sequence homology to any known Unigene. We initially named this gene FEST2 (fat EST2) and later omentin.

Sequence analysis revealed that full-length 1,269-bp omentin cDNA encodes a 313-amino acid protein. Analysis of the putative protein sequence suggested that the amino-terminal portion of omentin contains a highly hydrophobic region that is typical of a signal sequence for protein secretion and is likely to be cleaved between amino acids 17 and 18. The calculated molecular weight of the 296-amino acid-secreted peptide is 33 kDa. The amino terminus of the mature protein contains a region homologous to part of the fibrinogen-related domain, which is a globular structure and found in proteins such as the β- and γ-chains of fibrinogen, PGAR (peroxisome proliferator-activated receptor-γ angiopoietin-related) (41) and tenasin. In the course of functional characterization of omentin, several groups have reported the cloning of a gene whose protein sequence is identical to omentin under the names of intelectin (36), endothelial lectin HL-1 (27a), and intestinal lectin receptor (35). As implied by these names, the gene has been found to be expressed in intestinal and endothelial cells, thus suggesting more than one function. However, our studies show (see below) that the expression of this gene is greatest in visceral fat.

Omentin gene expression is fat depot-specific in humans and nonhuman primates. Northern analysis of multiple tissues indicated that omentin is highly expressed in human om fat, with much less in intestine, lung, and heart, barely detectable in muscle and kidney, and is not at all detectable in other tissues on the blot (Fig. 1A). Additional analysis demonstrated that this gene is expressed in om but not in sc adipose tissue (Fig. 1B). Conversely, leptin was more highly expressed in sc than in om fat, which is consistent with previously published findings (29, 30, 32). In addition, we studied omentin gene expression in rhesus monkeys. Again, in all of the 11 monkeys examined (5 shown in Fig. 1C), omentin was highly expressed in om fat but much less in sc fat from the same animals. Significant individual variation in omentin expression between animals was observed. On the basis of the relatively small number of animals studied, omentin mRNA levels by Northern analysis was not related to age, sex, fat mass, or glucose levels (data not shown). In mice, omentin mRNA was not detectable in sc, epididymal, retroperitoneal, or mesenteric adipose tissues. Very low amounts of omentin mRNA were present in periportal fat (Fig. 1D). By contrast, omentin mRNA was highly expressed in intestine, which is consistent with the reported expression pattern of intelectin (36), which is identical to omentin in sequence.

Omentin is expressed in adipose tissue stromal vascular cells. To examine which type of cell expresses omentin, we fractionated human om and sc adipose tissues into adipocytes and stromal vascular cells (SVCs) and performed qRT-PCR. As shown in Fig. 1E, omentin mRNA was ~350- and 150-fold higher in adipose tissue and SVCs, respectively, from om vs. the sc depot. Moreover, the omentin expression was higher in the SVCs than in the whole adipose tissue. There was a trace amount of omentin expression in om adipocytes, which is likely due to the residual SVC contamination of the adipocytes (24). These data indicate that SVCs are the predominant source of omentin in the adipose tissue. A large variance in omentin expression was observed in the subjects studied (female: age, 35–61 yr; BMI, 28–41 kg/m²), suggesting that omentin is subject to regulation and/or the variability in the sampling of omentin-expressing cells in humans. Immunohistochemical analyses were performed to determine the distribution of omentin protein within om and abdominal sc adipose tissues. Compared with preimmune serum, omentin antibody stained the small stromal cells between the large adipocytes in om fat (Fig. 2, A vs. B). Human om fat showed much greater omentin staining than abdominal sc fat (Fig. 2, C vs. D), which is consistent with our Northern and qRT-PCR findings. The modest omentin staining in sc fat is most likely derived from the circulation, considering the lack of gene expression of omentin in this depot.
Omentin is a secreted protein. To determine whether omentin is secreted, we overexpressed carboxy terminus-flagged omentin-F cDNA in mammalian HEK-293T cells. As shown in Fig. 3A, omentin-F is detected in both conditioned medium and cell lysates transfected with omentin-F cDNA, demonstrating that omentin is a secreted protein. To examine whether omentin is secreted from adipose tissue, we cultured human adipose tissue explants derived from omental or abdominal subcutaneous depots of 5 different humans. A band at the size of omentin was detected from the indicated fat depots and intestine in mice (pooled total RNAs of 5 mice). Because omentin is a secreted protein, we anticipated that omentin might be detectable in human blood. Plasma samples from three individuals were subjected to immunoprecipitation by omentin antibody or preimmune control serum followed by Western analysis. We detected a band corresponding to the size of omentin in the lanes treated with omentin antibody but not with control serum, indicating that the omentin-expressing cells either die or lose some or all of the biological features present in whole tissue ex vivo culture.

Fig. 1. Tissue-restricted expression of omentin mRNA. For all Northern analyses, 15 μg of total RNAs were blotted onto a nylon membrane and hybridized with radiolabeled omentin or leptin cDNA probes. RNA loadings were visualized by ethidium bromide staining. A: blot of multiple human tissues. Fat (O), omental adipose tissue. B: omentin and leptin mRNA expression in adipose tissue from omental or abdominal subcutaneous depots of 5 different humans. C: comparison of omentin expression between omental (O) and abdominal subcutaneous (S) fat depots from 5 obese rhesus monkeys. D: omentin mRNA expression in adipose tissue from the indicated fat depots and intestine in mice (pooled total RNAs of 5 mice). E: quantitative real-time PCR analysis of omentin gene expression in adipose tissue and fractionated adipocytes and stromal vascular cells (SVCs). Data are expressed as means ± SE, n = 5. *P = 0.016; **P < 0.01.
Omentin enhances insulin-stimulated glucose transport and Akt phosphorylation in human adipocytes. To functionally characterize omentin, we overexpressed recombinant omentin in human HEK-293T cells and purified the protein to homogeneity by chromatography (Fig. 4A). To investigate whether omentin affects insulin signaling, we tested the effect of omentin on insulin stimulation of glucose uptake in isolated human sc adipocytes. Omentin (300 ng/ml for 1 h) had no effect on basal glucose uptake. However, omentin significantly increased the effect of insulin-stimulated glucose uptake by 50 ± 11% (P < 0.01, n = 9). Thus the magnitude of insulin’s effect (% increase over basal) on glucose uptake was enhanced from 47 ± 10% (without omentin) to 105 ± 11% (with omentin) (P < 0.01, n = 9; Fig. 4B, a). We next examined the dose-response effect of omentin in adipocytes from a subset of five subjects and found that omentin at a concentration of 150 ng/ml was nearly as effective as that of 300 ng/ml [32 ± 8% (P < 0.05) at 150 ng/ml vs. 42 ± 11% (P = 0.01)] in stimulating glucose uptake (Fig. 4B, b). Omentin also stimulated insulin-mediated glucose uptake by om adipocytes (from 25 ± 2 to 34 ± 3 fl·cell⁻¹·s⁻¹, P < 0.05, n = 3). Interestingly, the magnitude of the omentin effect was higher in abdominal sc adipocytes than in om adipocytes of the two paired samples tested [subject 1: 43 (sc) vs. 25% (om); subject 2: 107 (sc) vs. 48% (om)], but this observation will require confirmation in a larger sample.

To understand possible mechanisms by which omentin potentiates insulin’s action, we investigated whether omentin modulated the phosphorylation/activation of Akt by insulin, a key molecule in insulin signaling. Isolated human sc adipocytes from a subset of five subjects and found that omentin at a concentration of 150 ng/ml was nearly as effective as that of 300 ng/ml [32 ± 8% (P < 0.05) at 150 ng/ml vs. 42 ± 11% (P = 0.01)] in stimulating glucose uptake (Fig. 4B, b). Omentin also stimulated insulin-mediated glucose uptake by om adipocytes (from 25 ± 2 to 34 ± 3 fl·cell⁻¹·s⁻¹, P < 0.05, n = 3).Interestingly, the magnitude of the omentin effect was higher in abdominal sc adipocytes than in om adipocytes of the two paired samples tested [subject 1: 43 (sc) vs. 25% (om); subject 2: 107 (sc) vs. 48% (om)], but this observation will require confirmation in a larger sample.

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cytes were treated with omentin for 0, 15, or 60 min followed by stimulation with insulin at increasing concentrations for 5 min (Fig. 5). Pretreatment with omentin for 15 min resulted in an activation of Akt in the absence of insulin (lane 2) or submaximal insulin concentration (60 pM, lane 5). However, this effect subsided after omentin treatment for 60 min, indicating that the effect is transient. Insulin alone (60 pM) marginally stimulated Akt phosphorylation (lane 4). However, the effect of a submaximal insulin concentration was greatly increased by omentin treatment (lane 5 vs. lanes 4 and 2; lane 6 vs. lane 3). At a maximal concentration (3.0 nM) of insulin, treatment with omentin did not further enhance insulin-stimulated Akt phosphorylation (lane 7 vs. lanes 8 and 9). Similar results were obtained in two additional independent experiments, suggesting that omentin increases insulin sensitivity.

**DISCUSSION**

Visceral obesity is more pathogenic than sc obesity in promoting insulin resistance, type 2 diabetes, and cardiovascular disease, presumably due to functional and/or anatomical differences between visceral and sc fat depots. In addition, visceral fat accumulation is associated with accumulation of triglycerides in muscle and liver, which may contribute to insulin resistance in these tissues. Toward a better understanding of the biology of human visceral fat at the molecular level, we conducted om adipose EST analysis and discovered a novel adipokine, omentin, which is selectively expressed in visceral fat. To our knowledge, omentin is among the first molecules to exhibit such a dramatic difference in gene expression between the two major fat depots. Furthermore, omentin is a secreted factor that enhances the effect of insulin action on glucose metabolism. As a secretory factor, omentin is a novel hormone that is likely to act as both an endocrine factor to modulate systemic metabolism, including insulin action in sc adipocytes, and an autocrine and paracrine factor to regulate visceral adipose biology locally.

Whether omentin is related to human obesity and insulin resistance is an important question. How omentin levels change in obesity is not yet known. Adipokine production can be either increased (e.g., leptin) or decreased (e.g., adiponectin) in obesity. Our studies have demonstrated that omentin enhances insulin action by stimulating insulin-mediated glucose uptake by sc as well as om adipocytes in vitro. The serum concentration of omentin determined by immunoprecipitation and affinity purification is ~100 ng to 1 µg/ml. Thus the concentrations that we used to show potentiation of insulin-stimulated glucose uptake most likely lie within the physiological range. Omentin is produced by visceral fat, and its local concentration in visceral fat may far exceed that in the circulation or in sc fat. Thus, on a local level, within the om adipose depot, omentin may act as a paracrine factor to enhance insulin sensitivity and glucose metabolism and thereby modulate the distribution of body fat between visceral and sc fat depots. On the other hand, because omentin circulates in blood, it may also act at distant sites, e.g., muscle, liver, and sc fat, to enhance insulin sensitivity and glucose metabolism, and thus may play a wider role in nutrient storage and partitioning. Sc fat comprises more than 80% of the adipose tissue in the human body. Hence, the fact that omentin circulates systemically and potentiates insulin action in sc fat may be of physiological and perhaps pathophysiological importance.

It is of interest to compare properties of omentin to visfatin, a recently described adipokine that was reported to be predominantly secreted from visceral adipose tissue in humans (15).
However, subsequent studies found no significant difference in vistatin gene expression between sc and visceral depots (4). Although its site of expression in human adipose tissue is unknown, visfatin is expressed in rodent adipocytes (23), in contrast to omentin, which is expressed primarily in adipose SVCs, at least in humans. Like omentin, visfatin modulates insulin action (15). However, omentin, unlike visfatin, enhances only insulin-mediated glucose transport and does not stimulate basal glucose transport on its own (Fig. 4B), indicating that omentin has no intrinsic insulin-mimetic activity. It is reasonable to believe that depot-dependent insulin action is subject to modulation by local hormones, growth factors, and adipokines. Further investigation is required to elucidate the role of individual adipokines, such as visfatin and omentin, in the development of obesity and type 2 diabetes.

We found that the effect of omentin on insulin-stimulated (60 pM) Akt phosphorylation was transient. Transient phosphorylation is often observed in signal transduction. For example, resistin transiently activates phosphorylation of the p42/44 mitogen-activated protein kinase (ERK1/2) in human aortic smooth muscle cells (9), and androgen induces rapid and transient Akt phosphorylation in MC3T3-E1 osteoblasts (20). The mechanism and relevance of the transient effect of omentin is not understood at present.

Omentin expression in stromal vascular cells is intriguing. Stromal vascular cell fraction in om fat tissue consists of a number of different cell types including preadipocytes, fibroblasts, endothelial cells, and macrophages. Which one of these cell types expresses omentin is presently not known and is the subject of further investigation. A clue comes from several laboratories that independently reported the cloning of intelecin (36), endothelial lectin HL-1 (27a), and intestinal lactoferrin receptor (35), whose protein sequences are identical to omentin. As implied by those names, the gene has been found to be expressed in intestinal Paneth (25) and endothelial cells. Whether there exists a unique type of cell in the om adipose depot or the unique local environment induces omentin expression from a known cell type is under investigation. Nevertheless, because secreted products of Paneth cells are released into the intestinal lumen, om fat is likely the major source of circulating omentin in humans. In addition, omentin is barely expressed in mouse adipose tissue, indicating that the protein may play a more significant role in adipose biology in humans than in mice.

It is interesting to note that the omentin gene localizes on a chromosomal region of 1q22–q23, where we (34) and others (11, 16, 38, 39) have reported linkage to type 2 diabetes in various populations. These data suggest that omentin may be a
positional candidate gene for type 2 diabetes susceptibility in humans (14).

In conclusion, we find that omentin, also named intelectin and previously known to be expressed in intestinal Paneth and endothelial cells, is a novel visceral fat depot-specific secretory factor. Omentin enhances insulin-stimulated glucose transport in sc as well as om adipocytes and may therefore be implicated in the pathogenesis of obesity and its comorbidities. Future analysis of omentin’s biological actions, and measurement of omentin levels in the om depot as well as in the circulation of humans with or without obesity and its comorbidities, will help to define its role in the pathogenesis of these diseases. Finally, omentin may serve as a probe for further understanding of the biological differences between om and sc fat.

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