Gene expression profile of omental adipose tissue in human obesity[1]

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SPECIFIC AIMS

The aim was to gain insight into the pathophysiology of obesity by comparing the pattern of gene expression of omental adipose tissue of obese and lean volunteers. Omental adipose tissue is more closely involved in the comorbidities associated with obesity than fat from the subcutaneous depot.

PRINCIPAL FINDINGS

Omental adipose tissue biopsies were obtained by laparoscopic surgery from six male patients (44.2±6.3 years). RNA was extracted and pooled for the normoglycemic, normotensive obese (BMI 37.3±2.5 kg/m^2), and lean (BMI 23.4±0.8 kg/m^2) groups, then hybridized to the HO1 Express Chip™ DNA Microarray System (Mergen Ltd.). Of 1152 well-characterized genes analyzed, 41% were expressed at sufficient levels in human adipose tissue for detection in the microarray experiments in addition to the 10% embodying housekeeping genes, duplicates, and negative controls. From the 153 genes with a >2.0-fold variation, 89 (8% of the total number) were up-regulated and 64 were down-regulated (**Table 1**).

1. The set of genes with altered expression in omental adipose tissue of obese humans represents a broad spectrum of biological processes

The majority of genes with altered expression encode proteins involved in cell proliferation, immune response, angiogenesis, metabolism, and signal transduction which have not been described to be involved in obesity.

2. Omental adipose tissue of obese humans exhibits an up-regulation of lipolysis repressor genes and a down-regulation of genes involved in lipolysis activation

Relevant genes involved in inhibition of the lipolytic rate such as neuropeptide Y (NPY) receptors Y1 (NPY1R) and Y5 (NPY5R) and adrenergic β receptor kinase 2 (ADRBK2) showed increased mRNA expression in obese patients (**Fig. 1**). Genes participating in the activation of lipolysis, such as natriuretic peptide receptor C (NPR3) and adrenergic β-2 receptor (ADRB2), showed decreased mRNA expression.

3. Omental adipose tissue from obese patients presents a decreased expression of growth factors and an increased expression of MAPKs

Expression of genes involved in preadipocyte proliferation and differentiation such as IGF1, FGF2, 4, and 7 was decreased. Several members of the mitogen-activated protein kinase (MAPK) cascade such as MAPK3, MAP3K4, MAPK9, and MAP2K6 exhibited increased expression.

4. Obesity alters the expression in omental adipose tissue of genes involved in angiogenesis

Of special interest were the changes observed in angiogenic factors. While vascular endothelial growth factor B (VEGFB) and fibroblast growth factor (FGF) 1 (FGF1) were up-regulated, c-fos-induced growth factor (vascular endothelial growth factor D) (FIGF) was down-regulated.

5. JAK2 expression is reduced in omental adipose tissue of obese humans

The mRNA abundance level of Janus kinase 2 (JAK2) was reduced in adipose tissue samples from obese patients vs. lean subjects.

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[1] To read the full text of this article, go to http://www.fasebj.org/cgi/doi/10.1096/fj.03-0591fje; doi: 10.1096/fj.03-0591fje

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TABLE 1. *Summary of genes with up- or down-regulated expression in human omental adipose tissue of obese individuals*

Biological process (GO)[a]	Fold	UniGene symbol	Name	Cytogenetic band
Up-regulated				
Cell proliferation	3.5	VEGFB	Vascular endothelial growth factor B	11q13
	2.9	FGF1	Fibroblast growth factor 1 (acidic)	5q31
Immune response	7.4	FCGR3B	Fc fragment of IgG, low-affinity IIIb, receptor for (CD16)	1q23
	4.1	FCGR2A	Fc fragment of IgG, low-affinity IIa, receptor for (CD32)	1q23
Metabolism	2.5	LRP5	Low density lipoprotein receptor-related protein 5	11q13.4
	2.4	ADRBK2	Adrenergic, beta, receptor kinase 2	22q12.1
	2.3	GSK3A	Glycogen synthase kinase 3 alpha	19q13.31
	2.1	PGK1	Phosphoglycerate kinase 1	Xq13
Signal transduction	5.6	MAPK3	Mitogen-activated protein kinase 3	16p12-p11.2
	3.1	NPY1R	Neuropeptide Y receptor Y1	4q31.3-q32
	2.8	MAP3K4	Mitogen-activated protein kinase kinase kinase 4	6q25.3
	2.4	MAPK9	Mitogen-activated protein kinase 9	5q35
	2.2	MAP2K6	Mitogen-activated protein kinase kinase 6	17q25.1
	2.1	NPY5R	Neuropeptide Y receptor Y5	4q31-q32
Down-regulated				
Cell proliferation	5.9	FGF4	Fibroblast growth factor 4 (heparin secretory transforming protein 1, Kaposi sarcoma oncogene)	11q13.3
	4.7	FGF2	Fibroblast growth factor 2 (basic)	4q26-q27
	4.1	IGF1	Insulin-like growth factor 1 (somatomedin C)	12q22-q23
	3.2	FGF7	Fibroblast growth factor 7 (keratinocyte growth factor)	15q15-q21.1
	3.0	FIGF	c-fos-induced growth factor (vascular endothelial growth factor D)	Xp22.31
Metabolism	3.0	LDLR	Low-density lipoprotein receptor (familial hypercholesterolemia)	19p13.3
	2.3	AR	Androgen receptor (dihydrotestosterone receptor; testicular feminization; spinal and bulbar muscular atrophy; Kennedy disease)	Xq11.2-q12
	2.0	PTGER3	Prostaglandin E receptor 3 (subtype EP3)	1p31.2
Signal transduction	3.3	IRS4	Insulin receptor substrate 4	Xq22.3
	3.2	NPR3	Natriuretic peptide receptor C/guanylate cyclase C (atrionatriuretic peptide receptor C)	5p14-p13
	2.9	JAK2	Janus kinase 2 (a protein tyrosine kinase)	9p24
	2.2	ADRB2	Adrenergic, beta-2-, receptor, surface	5q31-q32

[a] Genes were classified into categories depending on the putative biological process in which they are involved according to the classification used by the *Gene Ontology Consortium* (GO).

6. Obesity alters the expression in omental adipose tissue of genes involved in immune function

Our study shows the up-regulation of receptors for Fc fragment of IgG in adipose tissue of obese patients.

7. Distribution of differentially expressed genes according to the chromosome to which they are mapped reveals an unspecific pattern

Chromosomes 1, 11, and 19 showed the highest number of genes with changed expression in omental adipose tissue from obese patients; chromosomes 8, 13, 18, 21, and 22 were those to which fewer changed genes were mapped.

CONCLUSIONS AND SIGNIFICANCE

Given the epidemic proportions reached by obesity worldwide, there is a need for better understanding of dysregulated genes, which may be involved in its development. A key factor in energy balance is mobilization of lipids through lipolysis in fat cells; alterations in this process have been associated with obesity. Our study shows decreased expression of ADRB2 and increased expression of ADRBK2, a protein involved in the desensitization of β-adrenergic receptors. NPY, a neurotransmitter involved in food intake and body weight regulation, has been shown to be a powerful antilipolytic agent. Transcripts of the main receptors for NPY in body weight regulation (i.e., NPY1R and NPY5R) were readily detectable in our experiments in accordance with earlier reports. The expression of both genes was increased in adipose tissue samples of obese patients, suggesting an increased capacity of lipolysis inhibition that may contribute to obesity. The NPR3 is a receptor for the C-type natriuretic peptide (CNP) expressed in adipose tissue. Natriuretic peptides have been identified as a lipolytic pathway, with binding of CNP to its receptor exerting a lipolytic effect. The reduced mRNA expression of NPR3 detected in the

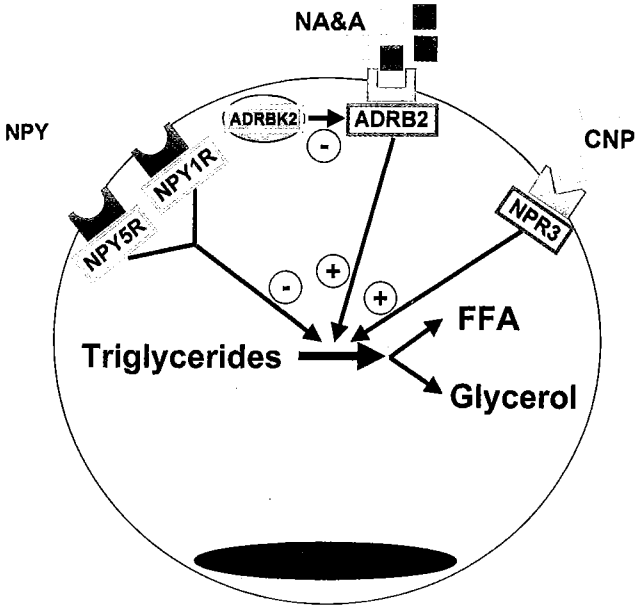

Figure 1. Summary of changes observed in the expression of genes involved in lipolysis of omental adipose tissue of obese subjects. Green frame indicates up-regulation in the expression of the respective gene; red frame stands for down-regulation.

present study is concordant with an impaired lipolytic activity in human obesity. These findings provide evidence for impaired lipolytic function in the obese subjects enrolled in our study that could either contribute to the development of obesity or represent an underlying mechanism of action of this disease.

Members of the FGF family showed decreased expression in obese patients indicating an attempt to decrease preadipocyte proliferation and adipocyte differentiation. Some MAP kinases were shown to be up-regulated, further supporting an inhibition of adipogenesis. This hypothesis is supported by studies reporting a decrease in the expression of genes normally involved in adipogenesis.

VEGFB and FGF1 induce vascularization by acting as endothelial cell growth factors. Obese patients had an increased expression of VEGF-B and FGF1 mRNA in omental adipose tissue, in accordance with the need for increased vascularization to support adipose mass enlargement.

Leptin signaling occurs mainly through activation of JAK2 and STAT3. JAK2 expression in adipose tissue of obese patients was decreased, which may be an indicator of leptin resistance, at least at the peripheral level.

Obese subjects have an impaired lymphocyte response, with decreased B and T cell function and low NK cell activity. Fc receptors are known to mediate antibody dependent inflammatory responses and cytotoxicity. Our data show that obese patients have an increased expression of a variety of Fcγ receptors and that adipocytes express a wide variety of genes involved in the immune response; this reinforces the link between adipose tissue and immunity.

To our knowledge this is the first study performed with humans in which obesity-induced gene expression changes were globally analyzed in omental adipose tissue by microarrays. Our data show that adipose tissue of obese patients exhibits a different expression profile from that of lean individuals. The high number and ample spectrum of genes changed in adipose tissue of obese patients substantiate a dramatically different obese adipocyte (**Fig. 2**). The complex and complementary nature of the expression profile observed in obese adipose tissue reflects a pleiad of adaptive changes affecting crucial physiological functions that may underlie the difficulties encountered by obese patients to lose weight. Our findings may have implications in identifying adequate molecular therapeutic targets. FJ

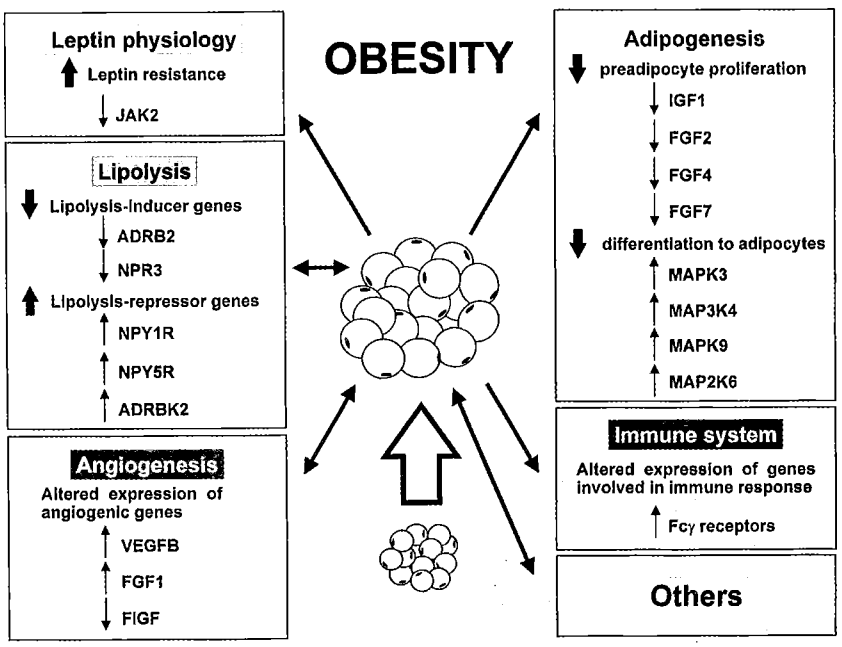

Figure 2. Schematic overview indicating genes that may be implicated in mediating the pathological consequences of obesity or involved in the genetic susceptibility to obesity.