Editorial

The Defense of Adipose Tissue against Excess Substrate-Induced Hyperthrophia: Immune System Cell Infiltration and Arrested Metabolic Activity

Marià Alemany

Department of Nutrition and Food Science, Faculty of Biology, University of Barcelona, Barcelona 08028, Spain; and CIBER Obesity and Nutrition, Institute of Health Carlos III, Spain

Obesity, the excessive accumulation of body fat, is a main defining feature of the metabolic syndrome, and overweight is often an early indication of the future severity and development of associated pathologies. There is a graded relationship between the increase in body adipose tissue content and the severity of insulin resistance, hypertension, and altered blood lipids, in addition to a number of additional disturbances in energy, nitrogen, and xenobiotic metabolism.

It is widely accepted that the manifestation of the metabolic syndrome cluster of diseases stems from the continued exposure to environmental factors [mainly diet, and especially fat intake (1)] modulated by genetic factors and epigenetic upbringing (2). Abundance of triacylglycerols in the diet translates into excess fatty acid availability, which in turn limits the utilization of dietary glucose by muscle and other tissues; we are adapted to first dispose of fatty acids for energy, preserving the glucose for the brain, as in starvation mode. Insulin resistance is, therefore a direct consequence of these preestablished priorities in the use of substrates under conditions of abundance of both carbohydrate and lipid.

Nonetheless, the primarily unused but readily available energy must be processed and/or disposed of somehow. This is accomplished by a number of partial solutions, including increased energy expenditure (thermogenesis, substrate cycling, and faster protein turnover), but the most immediate (and thrifty) solution is to store the excess energy as fat for eventual use under conditions of scarcity. This storage is widely distributed, including the liver, muscle, and other organs, but their overall cumulative capacity is limited. In contrast, adipose tissue's main function is precisely such caloric storage. Consequently, the adipocyte ends up with most of the surplus energy, largely because its barriers to prevent the accumulation of excess circulating glucose are not as effective as those that have been identified in muscle. The adipocyte incorporates fatty acids from lipoproteins and also takes a significant portion of the excess circulating glucose, which is used for lipogenesis and/or lactate production. Adipose tissue accumulation of excess triacylglycerols induces adipocyte hypertrophia, as well as relative hypoxia (in part due to tissue enlargement) (3) and acidosis because of glucose conversion to lactate (4).

The storage of surplus lipids in adipose tissue, however, cannot be sustained indefinitely— the tissue cannot grow to an impossible size, destabilizing the physiological systems and potentially placing survival at serious risk. One might consider massive obesity as propelling the body toward the verge of systemic physiological collapse. Because it is difficult to process a constant energy input surplus indefinitely, adipose tissue appears to react to such excess energy dumping as if it were an aggression to its integrity and function. This reaction is mainly carried out by at least three mechanisms: 1) decreasing cell metabolism, especially the entry of substrates, glucose utilization and lipogenesis, to limit the incorporation of more energy; 2) secreting of cytokine and other metabolic signals to correct hypoxia, reducing the excessive size of fat depots (including apoptosis), and dampening tissue reactivity to hormone signals (*e.g.* insulin) that facilitate fat deposition; and 3) increasing diapedesis to favor the massive infiltration of immune cells to fight the aggression through depression

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2010-2541 Received October 26, 2010. Accepted November 17, 2010.

For article see page E73

of cellular metabolism, the alteration of hormone signaling, the blockage of access to substrates, their uptake and accumulation, and inducing apoptosis and the arrest of cell differentiation and growth.

The well-known infiltration of macrophages (and their transformation) and of other cells of the immune system helps stem the growth of adipose tissue reserves but simultaneously results in the loss of the adipose tissue function as flexible energy storage buffer and depot. The whole set of defense reactions is akin to inflammation and extends its influence to surrounding organs (*e.g.* blood vessels, muscle) and to the body as a whole, helping to promote a systemic derangement—namely, the metabolic syndrome (5). Paradoxically, the initial objective of this response was to stop the pathological consequences of an indefinite accumulation of fat.

This is a situation in which the excess of energy in the form of dietary fats, but also of all other nutrients, overcomes our ability for energy storage, which was set for conditions that have evolved to protect us from starvation. In contrast, facing an excess of energy is a complete novelty from the point of view of the evolutionary struggle for survival. The logical reaction to this new challenge is the "preset" mobilization of defense systems. The result is to fight a problem of metabolic disarrangement with inadequate means, which were primarily designed to confront alien organisms and their proteins, not the energy substrates always sought for.

In the paper by Klimčáková *et al.* (6), published in this issue of *JCEM*, the careful analysis of the expression of omental and sc adipose tissue of humans reveals a remarkable convergence in the mechanisms of adaptation to the metabolic syndrome for both fat depots. In the two sites, there was a macroscopic advance of the disease along a series of human groups with varying degrees of adiposity (lean, overweight, obese, and obese with overt metabolic syndrome). These different grades of body fat were paralleled by an increase in the expression of genes related to immune defense and a fall in those linked to overall metabolism, including cell energy maintenance processes. Significantly, the pattern was the same for both adipose tissue locations despite small differences attributable to their developmental origin and physiological function.

The accumulation of excess fat in adipose tissue makes it not only dysfunctional but a potential hindrance to mobility and a source of metabolic misadjustment, irrespective of its location and the initial (*i.e.* normal) specific function of the site. The limitation of the extent of damage by preventing indefinite adipose tissue accumulation is coincident with the infiltration of immune system cells in adipose tissue. These cells are directly (or indirectly through their influence on adipocytes and stromal cells) responsible for the "cytokine storm" that extends to and beyond the adipose tissue masses and condition the development of the metabolic syndrome.

The sex-related differences in fat distribution correlate with a fairly different degree of severity of the metabolic consequences associated with excess fat accumulation. The android (or upper body) pattern, with a high predominance of visceral *vs.* sc fat, induces more intense deleterious change than the gynoid (or lower body) pattern. This has brought in the consequential idea that the presence of fat depots in different sites results in markedly disparate metabolic consequences. Most studies on adipose tissue changes and development of its alterations related to hypertrophia have been performed in rodents, and the distinct functions of their adipose tissue sites have been identified and characterized. However, there is not a direct correspondence between location and function in humans and rodents (*e.g.* the massive perigonadal fat pads of rats and mice and the practical quantitative irrelevance of these fat depots in humans). Most of the fat tissue present in the visceral cavity of obese rodents is not drained via the portal vein, in marked contrast to humans in which truly visceral adipose tissue is largely omental, closely related to the intestine. The differences between human and rodent adipose tissue distribution (and function) is an important caveat to the widespread assumptions that all adipose tissue sites placed inside the visceral space are equal and, consequently, functionally interchangeable.

The Klimčáková *et al.* (6) study confirms previous findings that uncomplicated obesity alone (*i.e.* the simple accumulation of fat) is not pathologically serious enough (7) to trigger a full response of the immune system. Then, what is the primary cause for the defensive reaction of adipose tissue to such excess energy aggression? And why is there a change in the expression of adipose tissue cells' metabolism toward a "minimum maintenance" status of cells already hypertrophied? In fact, and despite massive enlargement, adipose tissue cell sizes are different in different sites (8), and their actual metabolic response to hormonal stimuli is also distinct; however, all of them maintain the ability to carry on lipolysis and to metabolize glucose, largely to lactate.

Despite considerable work done on the mechanisms triggering (and maintaining) the inflammatory response in adipose tissue, we still don't know the precise sequence (and timing) of events for the development of this adipose tissue "malaise," which results in a partial loss of function as a consequence of its interaction with the immune cells. We can understand the infiltration as a response to distress signals (*e.g.* TNFα) from overstretched or hypoxic adipocytes. Their hypometabolic state may be a way to minimize their implication in energy metabolism that helps them

reject circulating substrates. However, this does not explain why all such processes do not also occur in "uncomplicated" obesity: the excess energy is present; the stimuli from damaged, overstretched, and hypoxic cells may be the same; but immune cell infiltration and its consequences are not observed. This may obviously be related in part to the development of the metabolic syndrome over time, which usually takes a significant number of years of nutritional aggression to become manifest.

The increased activation of glucocorticoids by adipose tissue, due in part to an increased expression (and activity) of 11β-hydroxysteroid dehydrogenase type 1 (9), may be in itself a sign of defense of the tissue against the excesses of the inflammatory response. This may be both a consequence of counterregulatory mechanisms to limit the extent of the immune system-driven reaction and an effect of the cytokine secretion defensive barrier altering the overall hormonal regulation of energy partition. However, this assumption does not explain why the simple sum of all these factors requires the additional passage of an inordinate amount of time to fully develop the metabolic syndrome.

In conclusion, the loss of adipose tissue function, its "occupation" by immune cells, and the ensuing alterations of cell apoptosis and oxygen supply (hypoxia, angiogenesis, blood flow control) seem a logical consequence of excessive fat accumulation. Often, however, obesity precedes the setting of a full-fledged metabolic syndrome, as shown by the Klimčáková *et al.* (6) study. It may seem that the response of adipose tissue (including the immune cell hosts) to the aggressive storage of energy is in itself a critical factor in the pathogenesis of the metabolic syndrome, but additional factors are needed to allow the full negative consequences of the metabolic syndrome to develop. The unveiling of these factors, probably endocrine, related to time (age) may help us to better understand the metabolic syndrome and set a solid basis for its treatment.

Acknowledgments

Address all correspondence and requests for reprints to: Marià Alemany, Ph.D., Department of Nutrition and Food Science, Faculty of Biology, University of Barcelona, Avenue Diagonal 645, 08028 Barcelona, Spain. E-mail: malemany@ub.edu.

The author's research is supported by a grant from the Spanish National Plan on Biomedicine and the CIBER Obesity and Nutrition.

Disclosure Summary: The author has nothing else to disclose.

References

1. **Axen KV, Dikeakos A, Sclafani A** 2003 High dietary fat promotes syndrome X in nonobese rats. J Nutr 133:2244–2249
2. **Steger DJ, Grant GR, Schupp M, Tomaru T, Lefterova MI, Schug J, Manduchi E, Stoeckert Jr CJ, Lazar MA** 2010 Propagation of adipogenic signals through an epigenomic transition state. Genes Develop 24:1035–1044
3. **Yin J, Gao Z, He Q, Zhou D, Guo Z, Ye J** 2009 Role of hypoxia in obesity-induced disorders of glucose and lipid metabolism in adipose tissue. Am J Physiol Endocrinol Metab 296:E333–E342
4. **DiGirolamo M, Newby FD, Lovejoy J** 1992 Lactate production in adipose tissue: a regulated function with extra-adipose implications. FASEB J 6:2405–2412
5. **Apovian CM, Bigornia S, Mott M, Meyers MR, Ulloor J, Gagua M, McDonnell M, Hess D, Joseph L, Gokce N** 2008 Adipose macrophage infiltration is associated with insulin resistance and vascular endothelial dysfunction in obese subjects. Arterioscler Thromb Vasc Biol 28:1654–1659
6. **Klimáková E, Roussel B, Márquez-Quiñones A, Kováčová Z, Kováčiková M, Combes M, Šiklová-Víktová M, Hejnová J, Šrámková P, Boloumié A, Viguerie N, Štich V, Langin D** 2011 Worsening of obesity and metabolic status yields similar molecular adaptations in human subcutaneous and visceral adipose tissue: decreased metabolism and increased immune response. J Clin Endocrinol Metab 96:E73–E82
7. **Wildman RP** 2009 Healthy obesity. Curr Opin Clin Nutr Metab Care 12:438–443
8. **Fried SK, Kral JG** 1987 Sex differences in regional distribution of fat-cell size and lipoprotein-lipase activity in morbidly obese patients. Int J Obes 11:129–140
9. **Morton NM** 2010 Obesity and corticosteroids: 11β-hydroxysteroid type 1 as a cause and therapeutic target in metabolic disease. Mol Cell Endocrinol 316:154–164