Putting Fat Cells Onto the Road Map to Novel Therapeutic Strategies

K. Alexander H. Iwen, Nina Perwitz, Daniel Kraus, Mathias Fasshauer, and Johannes Klein

The Inert Fat Cell: A Tale of the Past

In the wake of fighting the modern pandemic of obesity and its associated complications we are currently witnessing a paradigm shift in the appraisal of fat cell function. Until some ten years ago, interest into the investigation of fat cell function was mainly limited to those who wanted to find out more about mechanisms of lipid accumulation and lipolysis. For yet a smaller community of researchers, mechanisms of energy combustion in the form of heat generation, namely, "thermogenesis," was the reason to study so-called brown adipocytes which play an important role in enabling small vertebrates to survive in the cold. In 1994, the discovery of the fat cell-derived hormone leptin tantalized the scientific community worldwide and initiated a fundamental change in the apprehension of fat cell biology and regulatory circuits controlling energy homeostasis. Subsequently, an ever growing list of newly discovered adipocyte-derived factors, now commonly referred to as adipokines, prompted researchers to revise their classical notion of adipose tissue as an inert organ exclusively responsible for energy storage.

With every single newly discovered adipokine, interest into adipocyte function has been growing exponentially. Adipokines provide a molecular link connecting deranged energy storage and release to metabolic and cardiovascular co-morbidities. Moreover, adipocyte-derived factors appear to be critical to multi-system integrity including reproductive and immune system functions. Dysregulation of adipocyte function is now considered to be key to the pathogenesis of diverse metabolic and cardiovascular disorders. By the same token, this implies that modifying adipose tissue function may harbor a significant potential for treating a broad range of diseases (Klein et al., 2006). Here, we review recent advances in exploring fat cell-based treatment options. Furthermore, we propose a new concept of adipose tissue as a "critical link" organ that has evolved to better secure survival by a direct coupling of energy management to pleiotropic endocrine and immunoregulatory functions (Figure 1). This concept can guide novel approaches to explore the biology and therapeutic potential of adipocyte functions.

K. Alexander H. Iwen, M.D., Nina Perwitz, and Johannes Klein, M.D., Ph.D., are at the Department of Internal Medicine I, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany.
Daniel Kraus, M.D., is at the Department of Internal Medicine III, University of Frankfurt, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany.
Mathias Fasshauer, M.D., is at the Department of Internal Medicine III, University of Leipzig, Liebigstraße 27, 04103 Leipzig, Germany.
Dr. Klein's new address is Banting and Best Diabetes Centre, University of Toronto, Toronto General Hospital, 200 Elizabeth Street MBRW-4R402, Toronto, Ontario M5G 2C4, Canada.

Therapeutic Strategies

Modifying Lipid Accumulation in Fat Cells: Critical Signaling Systems and Transcriptional Factors

Energy storage in the form of lipogenesis is regulated by a number of traditional and newly discovered hormone systems. Membrane receptors or transcriptional factors that control lipid synthesis in fat cells may provide options to treat obesity or lipodystrophy/cachexia. Here, we describe receptors that are targeted by established or investigational drugs.

Insulin Receptor Signaling

Binding of insulin to its membrane receptor initiates a multi-step intracellular signaling cascade that mediates biological responses including glucose uptake, lipid synthesis, and cell proliferation. Interestingly, a fat cell-specific gene knock-out of the insulin receptor prolongs life and protects mice from obesity and glucose intolerance. Yet, a fat cell-specific disruption of the glucose transporter Glut4 renders mice insulin-resistant. The biologic consequences of an isolated defect in insulin action on the fat cell remain complex. However, components of the adipose insulin signaling system may provide an intriguing target to influence longevity, obe-

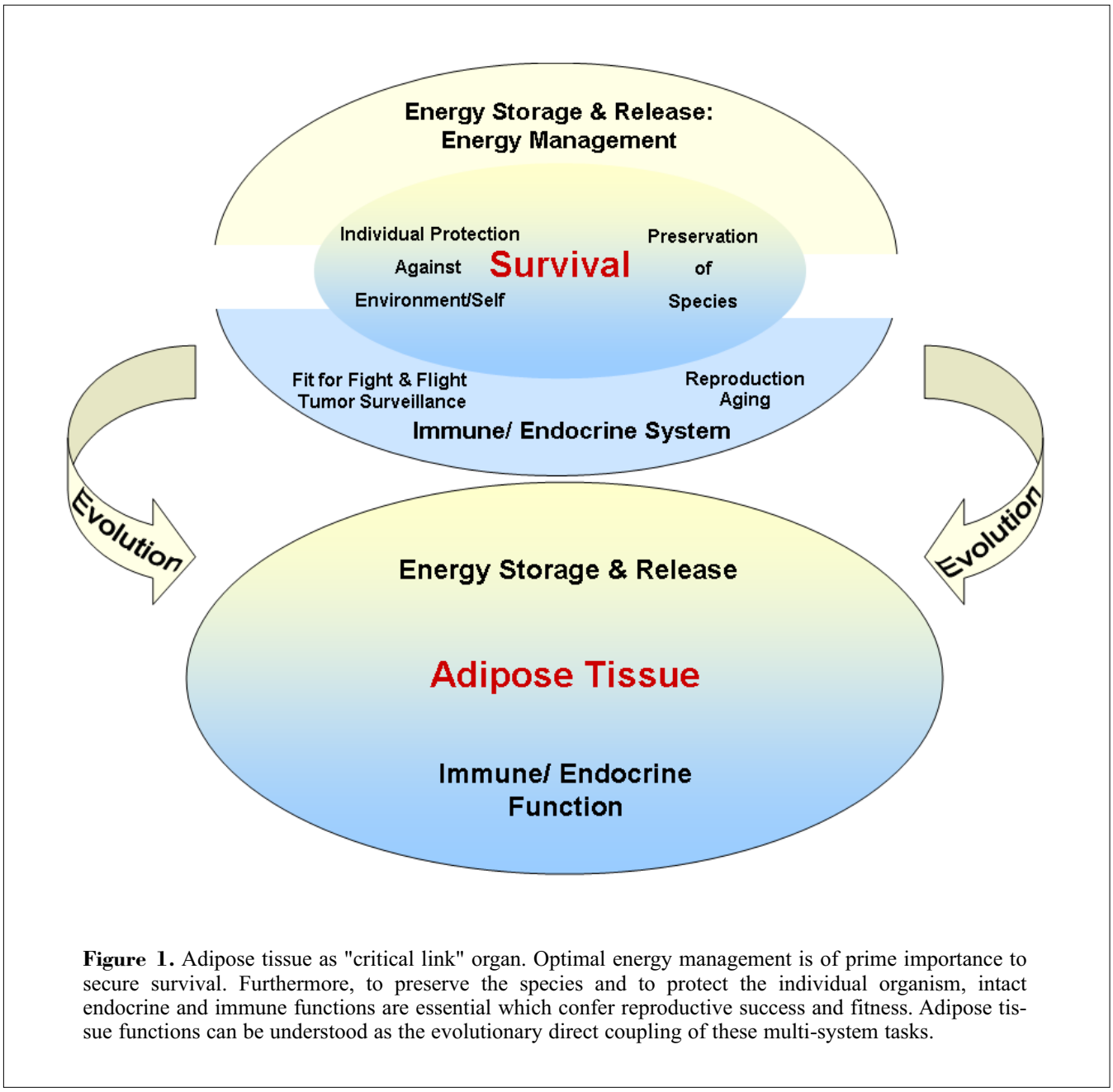

Figure 1. Adipose tissue as "critical link" organ. Optimal energy management is of prime importance to secure survival. Furthermore, to preserve the species and to protect the individual organism, intact endocrine and immune functions are essential which confer reproductive success and fitness. Adipose tissue functions can be understood as the evolutionary direct coupling of these multi-system tasks.

sity, and insulin resistance.

Endocannabinoid Receptor Signaling

The physiological basis for appetite-stimulating effects of cannabis plant extracts has recently been explained by the discovery of cannabinoid (CB) receptors and their endogenous ligands, the endocannabinoids. The endocannabinoid system controls energy homeostasis via both central and peripheral mechanisms and represents a novel target for anti-obesity treatment strategies. A number of recent studies report a direct CB1 receptor-mediated alteration of multiple fat cell functions including lipid synthesis, thermogenesis, and adipokine expression. The CB1 receptor blocker rimonabant induces weight reduction and improves cardiovascular risk factors in overweight patients in large clinical trials. In Europe and the USA, the drug is expected to be on the market in 2006. Further research into CB receptor-mediated changes in adipocyte function may help to identify novel mechanisms to treat cardiometabolic disease.

GIP Receptor Signaling

Glucose-dependent insulinotropic polypeptide (GIP) is an incretin hormone, i.e., it augments pancreatic insulin secretion when being released from the gut in response to food intake. GIP receptor activation in fat cells has been reported to promote lipogenesis. GIP receptor knockout mice are protected from high-fat diet-induced obesity. Adipocytes from these mice display a severe deficit in lipid accumulation. Taking into consideration these tissue-specific effects, both augmenting and antagonizing GIP actions are currently being discussed as therapeutic strategies to treat diabetes and obesity, and both GIP agonists and antagonists are under development.

Transcriptional Regulators

Among the transcriptional factors considered to be of pivotal importance to fat cell differentiation and lipid metabolism are the peroxisome proliferator-activated receptors (PPAR). Thiazolidinediones may serve as a proof of principle highlighting both the therapeutic potential and limitations of an approach that influences the energy storage capacity of fat cells. These so-called insulin sensitizers activate PPARγ, thereby ameliorating insulin resistance while, at the same time, inducing weight gain. Consequently, PPARγ antagonists are also under development to test their potential for treating obesity.

"Furthermore, we propose a new concept of adipose tissue as a "critical link" organ that has evolved to better secure survival by a direct coupling of energy management to pleiotropic endocrine and immunoregulatory functions. This concept can guide novel approaches to explore the biology and therapeutic potential of adipocyte functions."

Altering Heat Generation by Fat Cells: Inducers of Thermogenesis

A prerequisite for optimal energy management is the control not only of energy storage but also of its release. Specialized fat cells, so-called brown adipocytes, dissipate energy in the form of heat. The brown fat-specific mitochondrial uncoupling protein-1 (UCP-1) mediates the uncoupling of fuel oxidation from ATP generation. The disruption of the electrochemical proton gradient built across the inner mitochondrial membrane results in the release of thermic energy. This mechanism secures the survival of small mammals in the cold. Furthermore, this mechanism is physiologically employed to control energy homeostasis after food intake (diet-induced thermogenesis). However, brown adipose tissue is scarce in adult humans. Yet, strategies to activate brown adipocytes and to convert white to brown adipose tissue are being investigated as treatment options for the insulin resistance syndrome. For example, the β_3-adrenergic receptor that is predominantly expressed in adipose tissue is closely linked to the induction of thermogenesis in rodents. Nevertheless, the success of β_3-adrenoceptor agonists in humans has been very limited, most likely due to a number of problems including low receptor affinity and insufficient reactivation of "dormant" brown adipocytes. Other potential drug targets include molecular factors that induce a brown fat phenotype and thermogenic function. Interestingly, thiazolidinediones

appear to induce mitochondrial biogenesis in human fat cells. Adenovirus-mediated overexpression of the transcriptional coactivator PGC1α increases UCP-1 expression. Similarly, CNTF, an appetite-reducing factor, also directly induces UCP-1 expression, and a CNTF variant is currently being tested as a new anti-obesity drug in clinical trials. Finally, stimulation of the CB1 cannabinoid receptor directly inhibits UCP-1 expression which is in agreement with the beneficial effects of the CB1 receptor blocker rimonabant on energy homeostasis in humans. Conversely, cannabis and synthetic CB1 receptor agonists can be used to treat cachexia and to induce hypothermia.

Interacting With Multiple Organ Systems: Adipokine-based Approaches

Fat cell-derived factors exert a broad range of biological functions. Their pleiotropic roles highlight the intimate interconnections between adipose tissue function and multi-system integrity. Optimizing energy balance in response to different environmental conditions is of prime importance to survival, and it appears plausible to assume that an organism will adapt the activity of virtually every other physiological system to changes in the regulatory circuit of energy homeostasis. Adipokines are emerging as important messengers in this communication network. We will mention examples that are currently most prominent from a clinical perspective. This list must not be considered all-inclusive. Here, we discuss important adipokines in the context of major categories of biologic actions.

Effects on Energy and Glucose Metabolism

Many adipokines affect glucose and energy metabolism. Leptin can be seen as the prototypic example. To date, it is the most extensively studied fat cell factor that has assumed a role as a "jack of all trades." In a landmark study of mice with a homozygous deletion of the *ob* gene, administration of this adipokine resulted in a drastic reduction of obesity. Although it has become evident that simple leptin administration does not represent the "magic bullet" for the general treatment of human obesity, this adipocyte-derived product has been shown to be effective for treating congenital forms of obesity as well as diabetes, dyslipidemia, and non-alcoholic steatohepatitis in lipodystrophic patients.

Adiponectin, another adipose tissue-specific protein with structural homology to collagen, has been discovered as an endogenous "insulin sensitizer." In different mouse models, adiponectin reverses insulin resistance, ameliorates dyslipidemia, and induces weight loss.

Finally, glucocorticoids play a key role in adipose tissue metabolism and differentiation. The enzyme 11β hydroxysteroid dehydrogenase type 1 (11β HSD-1) converts inactive cortisone into active glucocorticoid metabolites and is expressed in adipocytes. When overexpressed in adipose tissue, this enzyme induces the complete clinical picture of the insulin resistance syndrome. Conversely, 11β HSD-1-deficient mice are resistant to diet-induced obesity. Selective inhibitors of 11β HSD-1 are being tested in clinical trials to treat insulin resistance. Furthermore, analogous to selective sex hormone receptor modulators, selective glucocorticoid receptor modulators may provide future treatment options.

Table 1. Obstacles to the Therapeutic Exploitation of Fat Cell Functions

Unresolved Issues	Potential Solution
Tissue and depot selectivity	Angiogenic Markers Exploitation of physical-chemical traits including specific cell surface markers
Adiposopathy	Combined modulation of different adipose functions: e.g., coupling of lipogenesis inhibition to lipid oxidation

Effects on Immune System, Inflammation, and Vascular Function

Effects on the immune system and inflammatory processes have been reported for a broad range of adipocyte-derived factors including leptin, adiponectin, and visfatin that was originally described as a pre-B-cell colony-enhancing factor. In fact, the term "adipokine" has been coined to indicate that many factors secreted by fat cells are inflammation-related peptides such as cytokines and cytokine-like molecules. An increasing list of these factors includes IL-6, IL-8, IL-10, TNFα, MCP-1, and others. Many of these molecules have since been implicated in the pathogenesis of obesity and atherosclerosis. In this context, it may suffice to mention adiponectin as an adipokine that appears to protect against atherosclerosis. Recombinant forms of adiponectin or agonists of the recently discovered adiponectin receptors may represent novel strategies to treat the insulin resistance syndrome and its cardiovascular complications. Potentially further influencing vascular function and tone are fat cell products and hormone systems such as plasminogen activator inhibitor (PAI)-1 and the adipose renin angiotensin system (RAS). Interestingly, recent studies report the secretion of factors from human adipocytes that stimulate aldosterone secretion. These so-called "adipotensins" could contribute to the association between obesity and hypertension and may become an interesting target for antihypertensive therapies.

Effects on Reproduction

Energy homeostasis and the control of reproductive

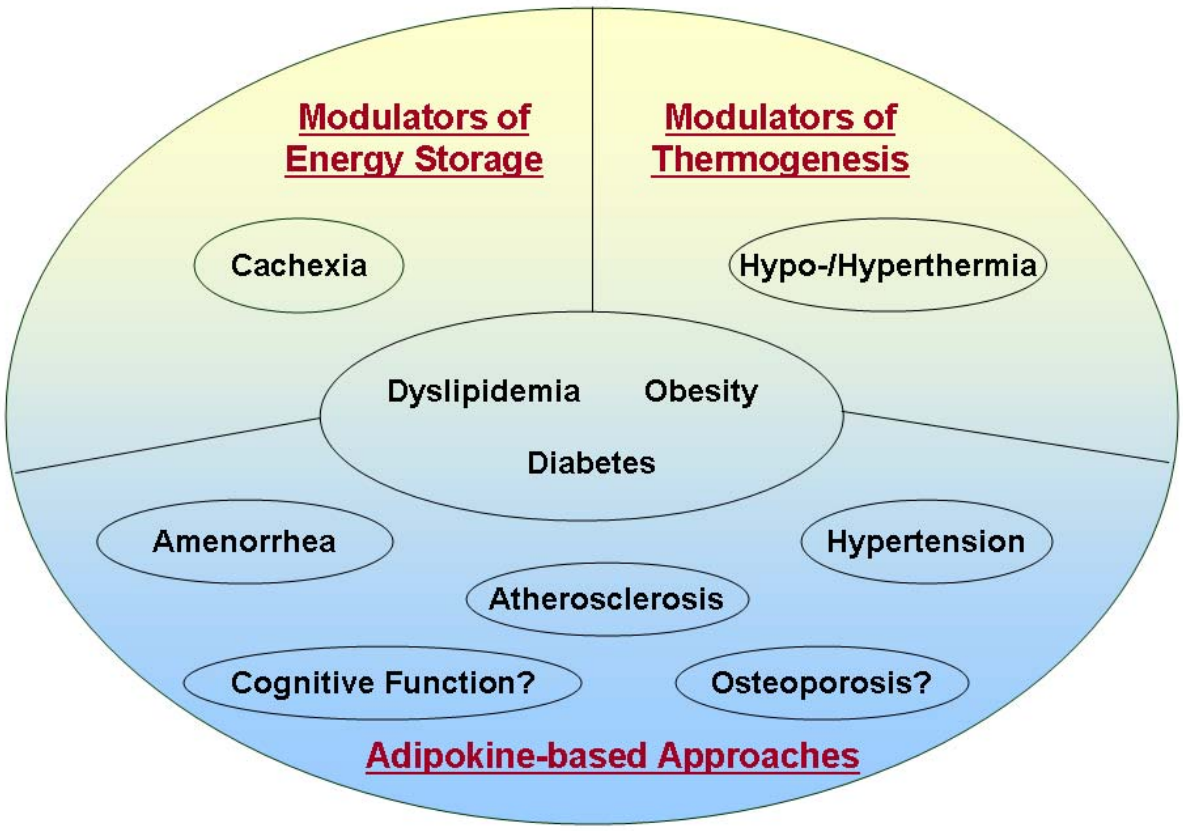

Figure 2. Current and potential adipocyte-based treatment options.

functions are closely intertwined. It is again leptin that has been studied best in this context. Leptin exerts a decisive role in sexual maturation. In a recent clinical example, it has been demonstrated that the administration of recombinant leptin to women with hypothalamic amenorrhea for three months restored ovulatory function and was accompanied by an improvement in thyroid and growth hormone axes, as well as markers for bone formation.

A Novel Concept of Fat Cell Function

The major biologic functions of fat cells so far delineated can be taken to illustrate one main task: to secure and enhance the chances of survival. First, in order to guarantee survival, it is of prime importance to optimize energy management. But what are further vital implications in a broader evolutionary context? On the one hand, an individual organism needs to be guarded against dangers from the "outside" or the "inside." This is guaranteed by an intact function of the immune system. On the other hand, reproduction needs to be secured in order to preserve the species. To this end, an intact endocrine function is a prerequisite. An organism affected by diseased immune and endocrine systems may be an easy prey because it is less fit to react with "fight or flight;" it may be prone to develop tumors because of a deranged tumor surveillance, and it may not be able to reproduce. Therefore, directly linking optimal energy management to intact immune and endocrine function is likely to be advantageous to survival. We propose that adipose tissue has evolved to serve exactly this purpose: i.e., to facilitate the direct coupling of these biologic functions (Figure 1). If this notion is correct, it can be predicted that adipose tissue-derived factors influence other biologic responses potentially enhancing fitness and survival. This concept can, therefore, guide further research into the biology of adipokines and may result in the discovery of novel treatment options. A provocative list of potential further adipokine-mediated actions may include influences on bone and muscular strength as well as cognitive function, just to name a few. Indeed, effects of leptin on osteogenesis have been reported; an adipose-muscle crosstalk has been partially elucidated with respect to insulin resistance; and recently, leptin has been revealed to be critical for the developmental programming of neural projections (Horvath and Bruning, 2006).

"In fact, the term "adipokine" has been coined to indicate that many factors secreted by fat cells are inflammation-related peptides such as cytokines and cytokine-like molecules."

Future Challenges and Perspectives

A Note of Caution

To modulate energy storage and release as well as endocrine and immune function of fat cells for therapeutic purposes, a tissue-specific approach may be preferable. Given that subcutaneous and visceral fat appears to differ in its functional activities, it may even be important to selectively target specific fat cell depots. This represents a major obstacle to the development of adipocyte-based therapies (Table 1). Potential solutions to this problem may come from the identification of adipose tissue-specific angiogenic markers or physicochemical traits and membrane receptors of adipocytes that can be exploited by circulating drugs or RNA interference strategies. Another problem of adipocyte-based therapies may be easier to overcome: the close interconnection of different levels of fat cell functions. A dysregulation on one level of fat cell function may cause a complex "adiposopathy." For example, inhibiting energy storage in adipocytes will most likely result in potentially adverse changes in the adipokine profile secreted. Furthermore, it may promote extra-adipose lipid deposition that would negatively influence insulin sensitivity. A "tailored" combined approach may therefore be needed that addresses several adipocyte functions at the same time. In this regard, thiazolidinediones and cannabinoid receptor blockers appear to show interesting activity profiles.

Plasticity of Fat Cells

Finally, another perspective of research on adipose tissue must not go unmentioned. Adipose tissue appears to be an interesting and easily amenable reservoir of stem cells with a high capacity to differentiate into multiple tissues (Tholpady et al., 2006). Thus, the (trans)differentiation of preadipocytes into neurons and osteoblasts has been reported. This potential has already successful-

ly been exploited to heal extensive calvarial defects by transplanting fat tissue.

In summary, a paradigm shift in the appraisal of fat cell function is beginning to yield fascinating insights into mechanisms interconnecting the control of energy homeostasis with longevity, tumorigenesis, immunity, reproduction, as well as many other physiological circuits. Further research on the biology of adipokines as well as on the regulation of energy storage and release in adipose tissue is likely to open up new avenues for the treatment of a broad range of disorders (Figure 2).

Acknowledgements

J.K. is a Feodor-Lynen fellow of the Alexander von Humboldt Foundation. This work was supported by the Deutsche Forschungsgemeinschaft.

References and Further Readings

Horvath TL, Bruning JC. Developmental programming of the hypothalamus: a matter of fat. *Nature Medicine* 12:52-53, 2006.

Klein J, Perwitz N, Kraus D, Fasshauer M. Adipose tissue as source and target for novel therapies. *Trends in Endocrinology and Metabolism* 17:26-32, 2006.

Tholpady SS, Llull R, Ogle RC, Rubin JP, Futrell JW, Katz AJ. Adipose tissue: stem cells and beyond. *Clinical Plastic Surgery* 33:55-62, 2006.