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Controversies in Experimental Dermatology

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What are subcutaneous adipocytes *really* good for…?

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Abstract: Our acute awareness of the cosmetic, psychosocial and sexual importance of subcutaneous adipose tissue contrasts dramatically with how poorly we have understood the biology of this massive, enigmatic, often ignored and much-abused skin compartment. Therefore, it is timely to recall the exciting, steadily growing, yet underappreciated body of evidence that subcutaneous adipocytes are so much more than just 'fat guys', hanging around passively to conspire, at most, against your desperate attempts to maintain ideal weight. Although the subcutis, quantitatively, tends to represent the dominant architectural component of human skin, conventional wisdom confines its biological key functions to those of energy storage, physical buffer, thermoregulation and thermoinsulation. However, already the distribution of human superficial adipose tissue, by itself, questions how justified the popular belief is that 'skin fat' (which actually may be more diverse than often assumed) serves primarily thermoinsulatory purposes. And although the metabolic complications of obesity are well appreciated, our understanding of how exactly subcutaneous adipocytes contribute to extracutaneous disease – and even influence important immune and brain functions! – is far from complete. The increasing insights recently won into subcutaneous adipose tissue as a cytokine depot that regulates innate immunity and cell growth exemplarily serve to illustrate the vast open research expanses that remain to be fully explored in the subcutis. The following public debate carries you from the evolutionary origins and the key functional purposes of adipose tissue, via adipose-derived stem cells and adipokines straight to the neuroendocrine, immunomodulatory and central nervous effects of signals that originate in the subcutis – perhaps, the most underestimated tissue of the human body. The editors are confident that, at the end, you shall agree: No basic scientist and no doctor with a serious interest in skin, and hardly anyone else in the life sciences, can afford to ignore the subcutaneous adipocyte – beyond its ample impact on beauty, benessence and body mass.

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Prelude 1

Adipose tissue has been neglected and misunderstood, at least in man (for it has long been known to be an energy resource for rats). What would women's journals write about if they had not heard of 'cellulite'? Even though they have got it wrong, 'Cellulite' is an 'invented disease' that only reflects a weak and aging dermis which allows fat to protrude and make the surface lumpy bumpy.

The long known functions of fat are listed in Table 1, and their relevance to the skin is reviewed elsewhere (1). More recently known are endocrine and cytokine production and the role of adipose tissue as a resource for stem cells.

But none of that explains the presence of *all that fat*, e.g. in the omentum or around lymph glands in the groin. Neither does it explain why antiviral therapy in HIV/AIDS causes havoc with body shape, with some sites atrophying and others showing disfiguring hypertrophy. Why is bone marrow replaced by fat cells as it ages, or why do lipomata arise sometimes from haematomata? Why do 100 000 000 persons accumulate fat in their lymphoedematous limbs (2)?

The questions continue: Why is so much tropical disease affecting the skin, focused on fat (3)? How come that the causative organism of leprosy lost most of that part of its genome that deals with lipid-metabolizing lipases and favours a dendritic cell that hugs the fatty myelin of nerves (4)? Why does the causative organism of the Buruli ulcer localize in adipose tissue (5)?

I have raised a question about the fat cells that are localized around adnexa and could favour bacteria inoculated by biting insects (3). Is the answer that stored in fat are a range of fatty acids any one of which is specifically and essentially required by at least one tropical organism? One no longer hypothetical example is the trypanosome of Chagas' disease which finds its specific fatty acid needs in the heart (6). I have asked whether the filaria of lymphatic filariasis choose the collecting lymphatics of the groin to grow microfilaria (is it because only there are the essential fatty acids they need, which are continually produced to feed the specific needs of inguinal lymphoid tissue?) (3).

It is Caroline Pond and her colleagues who have raised some of the most controversial issues in the adipose tissue fraternity (7–9). They say that dendritic cells and much of our immune system require very specific fatty acids and must induce a supply in their immediate neighbourhood. They do this by having control of the generation of fat and determining its fatty acid content and type.

Certain diseases are examples of an associated excessive induction of too great an amount of adipose tissue. They include exophthalmus, and Crohn's disease (10), the latter a clear example of lymphoid tissue associated with excess fat cells.

All of this exciting controversy is made more convincing by the realization that our ancestors made better use of fat to feed an immunosurveillance system (11). The earthworm's skin fights off earthen threats by using its skin and, thus, can do without a lymphatic system with lymph nodes to help recognize what is foreign and undesirable. Even earlier unicellular organisms evolved the cell membrane composed of cholesterol and phospholipids to incorporate proteins, fats and carbohydrate swinging between the cytosol and the external environment to help identify its needs and dislikes - a capacity that contemporary human biology has preserved in its own basic cellular structure and behaviour.

Now we have an epidemic of obesity that some believe is an inflammatory state and witness an era of detection and understanding of ancient cytokines. Apparently, it is tumor necrosis factor-α that helps to understand cachexia and weight loss in HIV/AIDS(12,13).

It is the contemporary generation of knowledge of genetics, growth factors and cytokines that almost daily turns our attention to the shamefully neglected role of stored fat.

Why should an inactivating mutation of VEGFR-3, which was first studied because it is linked to lymphatic function, produce obesity in a mouse (14)? Why should *Prox1*, a key transcription factor in lymphatic development, do the same (15)?

Energy production by lipase breakdown of fat storage is a 'common strategy' in a world of 'infrequent nutrient supply' (16). Dermatologists should ask why mutations in the catabolism of neutral lipid by lipases cause one genetic variant of ichthyosis (17). Unravelling this exposes complex interactions: for example, such interactions may also explain the acanthosis nigricans of some insulin-resistant conditions or the bizarre acanthosis of elephantiasis, which may perhaps have to do more with membrane remodelling rather than with energy production, and may be subject to the influence of catecholamines on adenyl cyclase and protein kinase A and cyclic AMP.

The epidermis needs fat (18) and dermatologists have long ignored that local availability of fat determines fast keratinization and several skin functions depend on it (1). Hence, specialised adnexa, the hair follicle, whisker and antler when attached to the sub-cutaneous tissue grow keratin, and its bloodsupply, under the influence of sex hormones, at a great rate.

Adipose cells are a gross example of lipid droplets, and their containment is everything but simple (17). There are several genes whose sole function is to regulate the surface proteins (appropriately named perilipins) on such droplets, which determine how droplet content is made available for metabolism.

I have long held that dermatologists give little credit and prefer not to own adipose tissue, just as when I began my

Table 1. Functions of adipose tissue

Energy provision
Thermoregulation
Insulation
Body contour
Endocrine
Cytokine and growth factor generation
Stem cells
Fatty acids for cell membranes and other specific functions of host and infective organisms

career they foolishly ignored blood vessels and later the lymphatics. The skin is peculiar in that, in health, it is mostly living without consuming oxygen. The epidermis is almost anaerobic. When it is in repair mode, however, switched on e.g. by transepidermal water loss and almost any injury, it becomes a factory for inflammatory mediators recruiting oxygen-demanding cells such as the neutrophil and oxygen-consuming activities such as mitosis and migration. It has to ensure adequate blood supply for repair and even makes a new organ known as granulation tissue. It does this while creating an improved lymphatic drainage system linked to macrophages and lymphoid cells with an immunosurveillance role. This process involving VEGF and hypoxia-inducing regulation of adipogenesis (19) results eventually in granulation tissue being turned into adipose tissue. It is surely possible that the demands of repair exceed supply in many forms of hyperkeratosis and parakeratosis. Likewise, chronic hypoxic injury inducing fatty acid release deserves investigation.

One other neglected theme is skin temperature – which is habitually low and similar to the metabolism of hibernation. Here, too, fat metabolism has much to tell us. The tropical diseases mentioned above, leprosy, Buruli ulcers, lymphatic filariasis or 'organs' such as granulation tissue would be best understood if all studies of the skin adopted temperatures that were lower than the core temperature of 37°C.

Now that dermatologists have become cosmetologists sucking out adipose tissue and placing it elsewhere with crude technology, enhancing the least of the fat cell functions to support body contour, they never think deeply about the cells on which they are practising genocide. Let me conclude this overture to a fascinating controversy in experimental dermatology, therefore, by reminding us that these abused cells have the potential to create an entire human being and that more careful dissection of their metabolism may help us to explain a majority of skin diseases.

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Prelude 2

Setting: Endocrinology and Metabolism Seminar, Department of Endocrinology, Poznań Medical University, Poland

Teacher.
Hello, everybody. As previously arranged, we are going to talk about subcutaneous adipocytes today, with all their pros and cons. Despite abundant anti-obesity media calls, obese people do exist, their number is growing, and, as long as they do not develop severe obesity complications, they usually represent the happier part of our society. Just listen to the Master from Stratford-upon-Avon:

Caesar:

Let me have men about me that are fat,
Sleek-headed men, and such as sleep a-nights:
Yond Cassius has a lean and hungry look;
He thinks too much: such men are dangerous.
William Shakespeare, Julius Caesar, Act 1, Scene 2

As Shakespeare noted, people with higher fat amounts may be trusted and are nice, and this paradox is obviously

contrary to the common concept of the obesity danger that we face in this century. Isn't it amazing? That's why I want you to focus on the role of subcutaneous adipocytes that may be the better part of our fat.

Lars (from Norway, loves dating Polish girls).
Well, sir, I find these subcutaneous adipocytes extremely important. The right amount of subcutaneous adipocytes and their proper function are most important for beauty. The female shape of the body is dependent as well on the subcutaneous fat distribution as on differences in skeletal construction. Moreover, this oestrogen-dependent subcutaneous fat distribution has at least one additional positive role: it seems to protect women from the dangerous consequences of obesity. Despite the generally high prevalence of coronary heart disease, diabetes, hypertension and other disorders that cluster into the metabolic syndrome in obese people, women with a relatively high amount of subcutaneous fat compared to visceral fat show much lower prevalence of coronary heart disease than men. As we know, men have less subcutaneous and more visceral fat (1,2).

Catherine (from the USA, her favourite leisure: reading psychological novels).
Actually, Lars, I really do appreciate your attitude, but still I find it rather narrow. To me, subcutaneous adipocytes are a big player in human behaviour, the thing noted by Shakespeare so long ago. Although obesity *per se* is associated with higher prevalence of depression, this is most probably the truncal, or visceral obesity, and subcutaneous adipocytes are really innocent here (3). Shakespearean Caesar prefers fat and happy companions and does not like lean Cassius, because Cassius is obviously stressed and depressed. Via a complex neurohormonal network, subcutaneous fat depots positively influence human psychology, especially acting on the serotonin-releasing brain neurones (4).

Ho-Lee (from China, likes neurology).
I agree with both of you, and I'll explain why: both intra-abdominal and subcutaneous fat depots are innervated by the parasympathetic and sympathetic nervous systems. It has been reported that decreased activation of the parasympathetic nervous system increases lipolysis and raises plasma free fatty acid levels, leading to insulin resistance in skeletal muscles and the liver (5). This results in the development of unwanted obesity complications.

In other words, not only the number of subcutaneous adipocytes, but also a predominance of sympathetic over parasympathetic activity that is observed in prolonged psychological stress and depression, could be the evil spirit of obesity complications. By the way, it is well known that prolonged stress increases the risk of coronary heart disease even in lean individuals, and as we know many stressed people are slim with poor subcutaneous fat depots. Just like our poor Shakespearean Cassius.

Thomas (from Germany, wants to go to the North Pole).
There's one thing we are not always aware of: slim people feel more cold than non-lean individuals with higher subcutaneous fat amounts. That is because of the process of thermogenesis and the presence of uncoupling proteins in the adipose tissue. Although the brown adipose tissue (BAT) is mostly found in newborn babies, it is still present between the predominant white subcutaneous adipocytes of adult humans, especially under the skin of the back and shoulders.

The discovery of cold-induced nonshivering thermogenesis and its location in BAT in the 1950s–1970s was followed by purification of the first uncoupling protein (UCP1), and later by cloning of the gene for UCP1 (6,7). Four more homologous proteins have been cloned, but their function remains unestablished: UCP2 (8,9), UCP3 (10–12), BMCP-1 (13,14) [also referred to as UCP5 by some authors (15)], and UCP4 (15,16). Current explanations for the functions of the newer UCPs assume that they uncouple oxidative phosphorylation, as does UCP1, and that they might therefore influence energy expenditure and energy balance. The candidate for a physiological phenomenon that might be mediated by one or more UCPs is the proton leak in mitochondria. However, there is so far no evidence that any UCP mediates the proton leak under physiological conditions (17,18). A new hypothesis by Himms-Hagen and Harper proposes a physiological role for uncoupling protein-3 (UCP3) in the export of fatty acid anions from BAT mitochondria when fatty acids are the predominant substrate being used (19). The hypothesis provides a logical explanation for the observed up-regulation of gene expression for UCP3 in brown subcutaneous adipocytes when fatty acid oxidation is stimulated, as during exposure to cold. It provides a plausible physiological role for UCP3 as a transporter protein, not as an uncoupling protein.

By the way, olive oil induces an up-regulating effect on UCP mRNA that is related to a local effect on adipose tissue (20).

So, you bet: when I go on my planned trip to the North Pole, I'm certainly going to take a large can of olive oil with me to help me fight that terrible cold over there.

Marcin (from Poland, interested in endocrinology).
Don't forget about our endocrine system. Subcutaneous adipocytes are hormone-dependent, and they are not only a passive fat depot but also a highly productive hormone factory (21). The balance between extra- and intra-adipose hormones may be the key factor in the regulation of both mood and body mass.

Hormones and cytokines produced by the subcutaneous adipocytes are termed adipocytokines. Among these adipocytokines, tumor necrosis factor-α, plasminogen activator inhibitor type 1, visfatin and some others increase the risk of obesity complications (22).

In contrast to these adipocytokines, adiponectin, an adipose tissue-specific, collagen-like protein, is an important antiatherogenic, antidiabetic and anti-inflammatory protein (23–28). Hypoadiponectinaemia is present in obesity, whereas higher levels of adiponectin are found in lean individuals. However, no matter how you try to explain it, this relationship is a paradoxical one: In simple words, the less fat tissue, the more adiponectin is generated by this tissue in the body. Following this rule, in cases lacking fat tissue completely, adiponectin concentrations would be extremely high – but the question of the source of its secretion would remain unsolved even then.

I feel that the only plausible answer may lie in the ratio of subcutaneous to visceral adipocytes, and in the balance between their activities. I even have my own hypothesis: subcutaneous adipocytes could be the main source of adiponectin, whereas an increased amount of visceral fat would lead to an inhibition of adiponectin production by means of some complex intra-adipose network.

Teacher.

So, in conclusion, the subcutaneous adipocytes are really necessary for a good mood, atherosclerosis protection and for keeping women 'more female'. Also, they warm-up our body and protect it from heat loss. In addition, they store energy, and they serve as both a hormone factory and a hormone user, in this way maintaining the hormonal homeostasis of the body.

Of course, every excess is harmful. In frank obesity, high amounts of subcutaneous adipocytes correspond to visceral obesity, which leads to benefit loss. Ontogenetically, the human being has always been fighting for food and preparing for long starvation, and maybe it is for this reason that we gain weight so easily. But in that same human species, for hundredthousands of years, the subcutaneous adipocytes have served as a vital energy store, as a heating machine, a female sexual attraction factor, and thus as one of the key factors for propagation of the species. So, maybe, we shouldn't complain too much when we fall prey to that dreaded, unsightly weight gain – after all, it may well have helped us to make it that far in evolution.

Now, I guess it's time for lunch.

But – please! – try not to overfeed yourselves, so as to keep your subcutaneous adipocytes in perfect balance…

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Viewpoint 1

Preconceived notions and evolutionary hardwiring

What are subcutaneous fat cells *really* good for? Let's face it: In these days of ever slimmer top models and 'fat-free-food' maniacs, the answer to this question must seem all too obvious to the worldwide increasing number of communities that fight soaring obesity levels and related co-morbidities: 'Fat is bad' is the permanently perseverated echo of media and press releases.

Yet, the very same question, perhaps omitting the attribute 'subcutaneous', would have been judged out of place in the times of Rubens and his peers. And, although we lack the privilege to admire similarly magnificent pictures, the same will have to be said, too, of earlier times, say 25 000 years BC, when statuettes like the 'Venus of Willendorf' were held in highest esteem (Fig. 1).

This is not a review about the history of mind and aesthetics on the perception of fat. But these eclectic examples – and it is quite simple to find more in other cultures and epochs – may reveal a deeper insight into some very timely issues: Fat tissue, since prehistoric times, has signified good health and fertility. And – certainly not only by chance related to this: Just try to imagine beauty and eros without fat tissue as modelling ingredience. Are aesthetics and physiology intertwined? Are there biological underpinnings to these age-old socio-cultural preconceptions?

In this viewpoint, we will argue that the subconscious notions of our ancestors about 'the importance of being fat' may be the result of evolutionarily hardwired wisdom. Ironically, it is only today, in the times of fat as the eminent public foe, that we begin to gain exciting insights into essential biological functions of fat cells.

Mighty matters: the right mass in the right place at the right time

To better define the frame for the topic at hand, let us first consider the extremes. In principle, the proneness to become fat may be taken as a case in point of its importance. The thrifty-genotype hypothesis invokes an evolutionary survival advantage for organisms capable of building energy stores quickly and efficiently (1,2).

Figure 1. Rubens: Venus and Adonis (left), Venus of Willendorf (right).

However, it is not infrequent that too much of a good thing amounts to a bad one, and fat tissue is no exception to this rule. Excess of intraabdominal (i.e. visceral) fat mass is associated with significant metabolic and cardiovascular disease, a main threat to modern affluent societies (3,4). However, intentional weight loss in overweight individuals *without* comorbidities may even increase mortality (5,6). Furthermore, with respect to subcutaneous fat, the jury is still out on its pathophysiological significance. Suffice it to say that, in subcutaneous locations, increased fat mass may even be beneficial (3,7–12).

Now, let's put the cart before the horse: What, if we did not have fat tissue at all? Coming from this other extreme, the answer appears clear-cut: We would not be better off. Lipatrophy and lipodystrophy result in severe metabolic and endocrine disease and premature death (13,14), not to mention the psychologically disturbing and socially negative disfigurement that comes along with it. Interestingly, implantation of fat tissue or administration of the fat cell-derived hormone leptin reverse or ameliorate these negative effects of fat loss (15,16).

Thus, it appears, as if nature aims at striking the right balance that guarantees a well-titrated mass of fat tissue in the right location (and, one should add, at the right time): Fat mass is subject to physiological, age-dependent alterations in babies, children and adolescents. We know very little about the significance of 'normal' fluctuations later in life. Studies suggest that cardiovascular risk and mortality associated with an increased fat mass also vary with age (17,18).

Taken together, the mechanisms critically determining fat distribution, depot-specific fat cell function, and age-dependent alterations of both, currently remain ill-understood. A complex interplay between environmental advantages (e.g. 'cutting a better figure' in an aqueous environment?) and endogenous factors (e.g. anatomical vicinity of metabolically active abdominal fat cells to the portal circulation of the liver?), can be hypothesized to have been at work in the progress of evolution.

In this context, the so-called brown fat also needs to be mentioned. This specialized thermogenic tissue typically resides in subcutaneous interscapular and interaxillar locations. It enables newborn mammals to survive in the cold by generating heat at the cost of ATP production (19). Albeit regressing with age, the calorie-burning brown fat, scattered between subcutaneous and intraabdominal white

fat cells, may be an interesting target for anti-obesity therapies – even more so, as transdifferentiation between energy-storing white and energy-combusting brown adipocytes does occur (20–22).

Transdifferentiation also provides the cue for the concluding note of this section: On closer inspection, fat tissue turns out to be a rather enigmatic mixture of different cell types, most likely of predominantly mesenchymal origin. Next to inflammatory cells, subcutaneous fat appears to harbour an interesting and readily amenable reservoir of precursor cells with an astonishing capacity to differentiate into multiple tissues (23). Thus, the (trans)differentiation of preadipocytes into neurones, myogenic and osteogenic cell lineages has been reported. Simple autologous transplantation of subcutaneous fat tissue has successfully been employed to heal extensive skull defects in mice and humans (24,25).

But now, let's turn to genuine metabolic and immunoendocrine fat cell functions in the following two sections.

Signalling in fat: connections to multisystem integrity and longevity

Tissue-specific genetic engineering techniques have recently provided the opportunity to gain unexpected insights into the biological role of intracellular signalling pathways in fat cells. Suffice it to list two instructive examples:

(1) Glucocorticoids play a key role in fat cell metabolism and differentiation (26). The enzyme 11β hydroxysteroid dehydrogenase type 1 (11β HSD-1) converts inactive cortisone into active glucocorticoid metabolites. When overexpressed in fat cells of transgenic mice, this enzyme induces the complete clinical picture of the metabolic syndrome with insulin resistance, obesity and dyslipidaemia (27). Conversely, the fat cell-specific genetic disruption of 11β HSD-1 or glucocorticoid inactivation conveys resistance against diet-induced abdominal obesity (28,29).

(2) Fat is a classical target tissue of insulin action (30). As fat tissue only takes up about 10% of the entire insulin-induced whole body glucose uptake, fat cell insulin sensitivity was not considered very important for overall glucose homeostasis. Yet, a fat cell-specific disruption of the glucose transporter Glut4 impairs insulin action in muscle and liver and renders mice insulin-resistant (31). In contrast, a fat cell-specific gene knock-out of the insulin receptor results in protection against obesity and against an age-dependent impairment of glucose tolerance (32). Another surprising finding is the increase in longevity by approximately 20% (33). In fact, insulin/IGF-1 signalling pathways in fat tissue have been implicated in regulating the life span even in ancient, evolutionarily distant model organisms such as worms and fruit flies (34).

In summary, the biological consequences of impaired signalling in fat cells remain complex. Yet, it has become evident that fat cell-specific alterations of intracellular signalling systems critically determine whole body energy homeostasis, lipid metabolism, insulin sensitivity and even longevity.

Fat cell products: networkers with therapeutic potential

Fat cells synthesize and secrete many lipid products and peptides, 'adipokines', which contribute to the control of a broad range of biological functions (35). This illustrates again the intimate interconnections between fat cell function and multisystem integrity. Optimizing energy management in response to changing conditions of food supply is pivotal to survival. Thus, it is reasonable to assume that an organism will adapt the activity of virtually every physiological system to maintain energy balance.

Adipokines are emerging as important messengers in this communication network. In addition to the control of energy and glucose homeostasis, studies on an incessantly growing list of adipokines have unravelled direct influences on immune system function and inflammatory processes, atherosclerosis, haemostasis, blood pressure regulation and fertility, just to name a few (36,37). Examples for the clinical exploitation of fat cell factors are the successful treatment of monogenic obesity (38), lipatrophic diabetes (16) and hypothalamic amenorrhoea (39) by administering the prototypic fat cell-derived factor leptin. Next, the insulin-sensitizing hormone adiponectin and other adipokines are waiting in the wings for diverse therapeutic applications (21).

A new concept of fat cell function

As delineated above, recent discoveries have assigned fat cells an essential role in the control of vital physiological circuits, including energy homeostasis, reproduction and longevity. Based on these findings, a concept of fat tissue as a 'critical link' organ can be developed.

Alright, you may say: In order to guarantee survival, it is of prime importance to optimize energy management. But, what are the further implications in a broader evolutionary context? Consider this: On the one hand, an individual organism needs to be protected against dangers, both from the 'outside' and the 'inside'. An efficient defence against infections and internal 'tumor surveillance' are managed by a vigilant immune system. On the other hand, species-specific genes 'want' to be preserved. To this end, successful reproduction is a prerequisite matched by an intact endocrine system. What could go wrong, otherwise?

An organism suffering from diseased immune and endocrine systems may be an easy prey because it is less fit to react by 'fight or flight'; it may be prone to develop tumours because of a deranged tumor surveillance, and it may not be able to reproduce. Therefore, linking energy

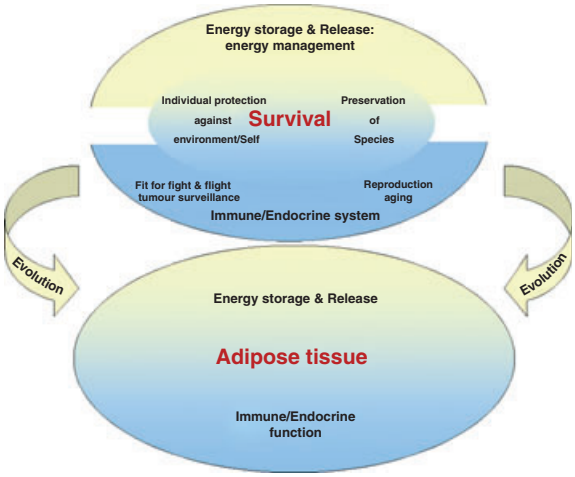

Figure 2. Concepts on fat cell function: adipose tissue as 'critical link' organ. Optimal energy management is of prime importance to secure survival. Furthermore, to preserve the species and to protect the individual organism, intact endocrine and immune functions are essential which confer reproductive success and fitness. Adipose tissue functions can be understood as the evolutionary direct coupling of these multi-system tasks.

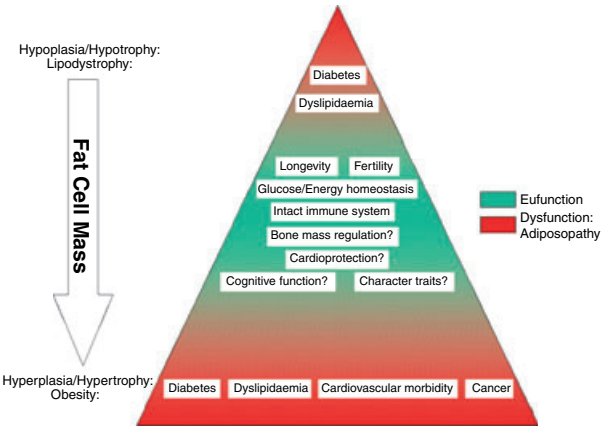

Figure 3. Proven and proposed fat cell functions.

homeostasis to an intact endocrine and immune system represents an evolutionary advantage.

We propose that fat cells meet exactly this challenge: They provide the direct coupling of energy management to immuno-endocrine regulatory functions (Fig. 2). They have evolved as 'guardians of multisystem integrity', thereby enhancing chances of survival.

This concept guides future approaches to discover new biological functions and fat cell-based therapies. For example, if this notion is correct, it can be predicted that fat cell-derived factors influence other physiological systems – potentially enhancing fitness and survival. A provocative list includes regulation of muscle and bone mass, cardioprotection and cognitive function. Indeed, an adipose–muscle crosstalk has been partially elucidated with respect to insulin sensitivity (31,40), effects of leptin on bone mass (41) and myocardial infarct size (42) have been reported, and finally, leptin has been revealed to be critical for the developmental programming of neural projections (43,44).

Perspectives: Shakespeare and beyond

So, did anyone *really* ask the question what subcutaneous fat cells are good for? Well then, this may pass for an answer: Fat cells make us fit for fight or flight, they protect us against metabolic, endocrine, immune and cardiovascular disease, they help us reproduce, and they assist in building our central nervous system synapses (Fig. 3).

We have already seen first examples of experimentally and clinically successful therapeutic uses of fat cell products such as leptin and adiponectin for seemingly unrelated metabolic and endocrine disorders (21). New indications along the paths outlined above may soon follow. And last but not least, fat depots harbour precursor cells with a clinically proven potential to transdifferentiate.

Given all this, the glowing appraisal that fat tissue has received from our ancestors, may indeed subconsciously have been based on nuts-and-bolts biological facts. Therefore, to close with Shakespeare's famous quote on the purported virtues of 'fat men' from Julius Caesar (see Prelude 2), we would not be surprised to learn, one day, that fat cell products contribute to modulating our sleep, character traits and social behaviour.

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Viewpoint 2

As the outermost protective barrier of our body, the skin consists of three layers: epidermis, dermis and a subcutaneous layer composed of mainly adipose tissue. Studies on the role of subcutaneous adipose tissue in dermatology have primarily focused on its thermoregulatory functions (1), and more recently, on its cosmetic effects as the major component of cellulite (2). However, adipose tissue may have more dynamic functions in skin physiology and pathophysiology.

Similar to the epidermis, adipose tissue has recently been shown to secrete various bioactive proteins. In the epidermis, keratinocytes act as the main source of these proteins, whereas many proteins secreted by the adipose tissue originate primarily from a mixture of adipocytes and non-adipocyte cell types in the tissue, including adipocyte precursor cells, macrophages and stromal vascular cells (3). As shown in Table 1, adipose tissue produces apparently unique proteins, such as acylation-stimulating protein (4), adiponectin (4) and resistin (4). The tissue also secretes angiotensin (4), leptin (5) and plasminogen activator inhibitor 1(6). These latter proteins may be less adipose-specific than generally thought, because keratinocytes also produce them (7–9).

Recent data suggest that an equally important, yet not well-recognized function of subcutaneous adipose tissue is to detect and to respond to pathogens in deeper tissues that have escaped the inflammatory processes initiated by the epidermis. By producing various interleukins (Table 1), subcutaneous adipose tissue may regulate B- and T-lymphocytes in concert with the epidermal keratinocytes. For example, adipose tissue produces interleukin-6 (IL-6) that promotes the differentiation of B lymphocytes (10). Adipose tissue releases IL-1 (11,12) that activates T cells to produce the autocrine T-cell growth factor, IL-2 (13), and the tissue also produces the IL-2-like cytokine, IL-15 (14). Although it is not known whether this tissue can release IL-12, it does produce IL-18 (15) that, similar to IL-12, stimulates T cells to produce γ-interferon (IFN-γ), a factor promoting optimal expansion of antigen-specific T cells (16). In addition, adipose tissue also modulates the fatty acid composition of lymph node dendritic cells (17) that may alter their antigen-presenting function. Furthermore, adipose tissue can release immune-suppressing cytokines, e.g. IL-10 (18) and TGF-β (19), that down-regulate lymphocyte responses.

Adipose tissue produces other inflammatory cytokines, such as tumor necrosis factor- α (TNF-α) (20), that may help fight invading bacterial pathogens, but its ability to produce interferon in response to viral infections is, as yet, unknown. To help eliminate pathogens, adipose tissue faci-

Table 1. Comparison of the cytokine profiles produced by adipose tissue cells and keratinocytes

Cytokines	Adipose cells	Keratinocytes	References
'Adipose-specific' factors			
Acylation-stimulating protein	+	ND	(4)
Adiponectin	+	ND	(4)
Angiotensin	+	+	(4,7)
Leptin	+	+	(5,8)
Plasminogen activator inhibitor-1	+	+	(6,9)
Resistin	+	ND	(4)
Interleukins			
IL-1α	+	+	(11,39)
IL-1β	+	+	(12,40)
IL-1RA	+	+	(41,42)
IL-3	ND	+	(43)
IL-6	+	+	(10,44)
IL-7	ND	+	(45)
IL-8	+	+	(21,46)
IL-10	+	+	(18,47)
IL-11	ND	+	(48)
IL-12	ND	+	(49)
IL-15	+	+	(14,50)
IL-18	+	+	(15,51)
IL-19	ND	+	(52)
IL-23	ND	+	(53)
Other major inflammatory cytokines			
IFN-α, IFN-β	ND	+	(54)
TNF-α	+	+	(20,55)
Additional chemokines			
Eotaxin	+	+	(22,56)
Interferon-γ-inducible protein 10	+	+	(25,57)
MCP-1	+	+	(23,57)
MCP-3	+	+	(23,58)
MIF	+	+	(26,59)
MIP-1	+	+	(24,60)
MIP-2	+	+	(61,62)
MIP-3	ND	+	(63)
RANTES	ND	+	(57)
Additional growth factors			
Angiopoietin-1	+	+	(32,64)
Basic fibroblast growth factor	+	+	(28,65)
Endothelin-1	+	+	(61,65)
Epidermal growth factor	ND	+	(66)
Epidermal growth factor-like GF	+	+	(31,67)
Fibroblast growth factor-2	+	+	(29,68)
G-CSF	ND	+	(69)
GM-CSF	ND	+	(70)
Hepatocyte growth factor	+	+	(34,71)
Insulin-like growth factor	+	+	(30,72)
M-CSF	+	+	(27,73)
Nerve growth factor	+	+	(35,74)
Platelet-derived growth factor	+	+	(61,65)
Stem cell factor	ND	+	(65)
TGF-α	+	+	(36,66)
TGF-β	+	+	(19,75)
VEGF	+	+	(33,76)

ND, not determined; GF, growth factor.

litates recruitment of phagocytes and lymphocytes by producing chemokines, e.g. IL-8 (21), eotaxin (22), MCP-1 and MCP-3 (23), MIP-1 (24), and IFN-γ-inducible protein 10 (25). To specifically recruit and retain monocyte-derived macrophages, a component of adipose tissue as noted above, the tissue produces MIF (26) and MIP-1 that may cause monocytes to slow their migration, allowing M-CSF to exert its effects in differentiating them into tissue macrophages (27).

Immune responses within the skin layers can lead to tissue damage that is critical to resolve. Subcutaneous adipose tissue produces a number of growth factors that may contribute not only to the healing of the dermis and epidermis but also to maintain its complex cellular network, such as fibroblast growth factors (28, 29), insulin-like growth factor (30), and epidermal growth factor-like growth factor (31). As a highly vascular organ, adipose tissue also secretes growth factors to promote the growth of vascular endothelial cells and smooth muscle cells, such as angiopoietin-1 (32), VEGF (33), and hepatocyte growth factor (34). Angiotensin produced by adipose tissue (4) and keratinocytes (7) may help control local blood flow once the vessels have formed. The production of nerve growth factor by the adipose tissue promotes nerve growth which usually parallels the growth of blood vessels (35). The production of TGF-α by adipose tissue (36) adds a growth-enhancing activity for all of the above processes. Taken together, adipose-derived growth factors likely facilitate expedient recovery from damage in all layers of the skin.

The ability of subcutaneous adipose tissue to contribute to immune responses can be a double-edged sword. Specifically, functional dysregulation of this tissue not only impairs the process of mounting or resolving immune responses, but may also elicit unwanted consequences, such as the promotion of skin diseases and cancer. For example, in various types of panniculitis or inflammatory diseases of the adipose tissue as well as lymphoma of the skin, the local adipose tissue exhibits significant leucocyte infiltration (37). Adipose tissue is often considered to be an innocent bystander in these diseases. However, considering all of the pro-inflammatory molecules and growth factors that can be produced by this tissue (Table 1), perhaps adipose tissue may not be so innocent after all.

The adipose tissue production of growth factors may contribute to the vertical growth phase of primary melanomas and growth of local metastases through a downward-oriented cytokine gradient. In fact, higher adipocyte content in melanoma tumors correlates with increased melanoma metastatic potential and decreased survival rates of patients (38). Such a hypothetical cytokine gradient may also promote deep infiltration by basal cell and squamous cell carcinomas as well. As a potential mediator of various

skin diseases, further investigations are warranted into the specific bioactive proteins or other factors, cell types, and cell interactions of subcutaneous adipose tissue involved in promoting such disorders.

In summary, on the one hand, subcutaneous adipose tissue participates with the epidermis as an under-appreciated part of the innate immune system to fight invading pathogens and helps resolve injury as a source of inflammatory cytokines and growth factors. However, on the other hand, the growth factors produced by adipose tissue may make it an unrecognized promoter of skin diseases, particularly cancer progression.

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Viewpoint 3

Some men see things as they are and say: 'Why?'
I dream things that never were and say: 'Why not!'
John F. Kennedy

Adipocyte function in experimental (and translational) dermatology? Perhaps, this question better reflects the state-of-the-science if it is modified into an examination of *adipose tissue functions*. We must keep in mind that not only adipocytes themselves, but also other cellular components of adipose tissue may contribute to a possible endocrine and paracrine impact by this tissue on cutaneous health and disease, as has already been reported for a variety of other diseases (1–8).

Be this as it may, Giorgio Amendola and Giorgio Napolitano were frequently seen together in the Italy of the 1960s, and were jokingly called by their friends *Giorgio 'o chiatto* and *Giorgio 'o sicco* (for "Giorgio the fat" and "Giorgio the slim", respectively). Arguably, his "'o sicco" status is why Giorgio Napolitano, at 81 years of age, is still in a good body-and-mind health, and just got elected President of Italy. If you buy this argument, the power of adipose tissue is not to be underestimated. At least in Italy.

Since 1 December 1994, which is the public birthday of the adipocyte-secreted cytokine leptin (from Greek *leptos*, means slim) (5), the simple paradigm of adipocytes as mere fat storage cells has rapidly been evolving into a complex paradigm of endocrine and paracrine activities of these cells. Overall, this intellectual process framed a novel field of study named adipobiology by us (2) or adiposcience by Japanese (3).

Besides their important role in lipid and energy homeostasis, adipocytes, particularly white adipocytes, are *bona fide* protein-secreting cells using endo-, para- and autocrine pathways (2–4,6–9,13). In effect, adipocytes and other cells, such as those derived from adipose tissue stromovascular and matrix fractions (1,13), including the associated macrophages (6) and mast cells (2,7), secrete a large number (approx. 100) of multifunctional proteins, collectively designated adipokines by us (2,7,13, also see 9–12) or adipocytokines by Japanese (3,4,8). Table 1 shows a list and cellular sources of selected adipokines.

Despite impressive progress in the adipobiology of obesity and related cardiometabolic diseases such as type 2 diabetes, atherosclerosis and metabolic syndrome (1–4,6–8,13), our knowledge of cutaneous adipobiology is still very limited at present. Table 2 presents a list of skin diseases known to associate with altered levels of nerve growth factor (NGF), a neurotrophin that, besides its nerve growth stimulatory effect, may modulate various inflammatory, immune and metabolic processes (1,2,10–16). Whilst adipose-derived NGF (the adipokine NGF) exerts its neurotrophic (17,18) and angiogenic (19) effect, it is not known whether any extraneuronal actions may also be executed by this adipokine.

However, we do know that neonatal adipocytes and myofibroblasts of subcutaneous adipose tissue (SCAT) express NGF mRNA and NGF protein, thus contributing to more efficient wound healing in neonatal vs. adult rats (20). Fur-

Table 1. Selected list of adipokines[1]

Adipocyte-secreted adipokines
Adipsin, leptin, adiponectin, visfatin
Acylation stimulating protein, metallothionein-I, -II
Adrenomedullin, NGF[2], TWEAK[2]
Stromovascular cell- and/or matrix cell-secreted adipokines
Cytokines
Interleukin-1 (IL-1), IL-1 receptor antagonist, IL-6, IL-10, IL-18
Tumor necrosis factor-α, leukaemia inhibitory factor, oncostatin M
Macrophage migration inhibitory factor, NGF[2], TWEAK[2]
Chemokines
MCP-1 (CCL2), IL-8 (CXCL8), Eotaxin (CCL11)
RANTES (CCL5), IP-10, SDF-1 (CXCL12)
Growth Factors
FGF, TGF-β, CNTF, MCSF, BMP-2, HB-EGF, IGF, HGF
Angiogenic factors
Vascular endothelial growth factor, angiogenin, angiopoietin-2
Renin–angiotensin system
Renin, angiotensinogen, angiotensin I, II, aldosterone, chymase
Acute phase reactants
Serum amyloid A, lipocalin, ceruloplasmin
Haemostatic factors
Plasminogen activator inhibitor type 1, tissue factor
Others
FIZZ-1, resistin (FIZZ-3), omentin, apelin, vaspin, prolactin, somatostatin
agouti protein, prohibitin, calcitonin, calcitonin gene-related protein
Urocortin, retinol-binding protein-4, pigment epithelium-derived factor
Hypoxia-inducible factor-1α, oestrogen

MCP-1 (CCL2), monocyte chemoattractant protein-1 (cysteine-cysteine modif chemokine ligand 2); RANTES, regulated on activated normal T-cell expressed and secreted; IP-10; interferon-γ-inducible protein-10; SDF-1, stromal cell-derived factor-1; FGF, fibroblast growth factor; TGF-β, transforming growth factor-beta; CNTF, ciliary neurotrophic factor; MCSF, macrophage colony-stimulating factor; BMP-2, bone morphogenetic protein-2; HB-EGF, heparin-binding EGF-like growth factor; IGF, insulin-like growth factor; HGF, hepatocyte growth factor; FIZZ, found in inflammatory zone.

[1]Information for most of the listed adipokines derives also from recent proteomic analyses (41,42).

[2]Given as examples for a differential topogenesis of adipokines, such as NGF (1) and TWEAK (TNF-like weak inducer of apoptosis), a pro-inflammatory cytokine of the TNF family (26).

Table 2. NGF-related skin diseases, as a possible target for adipobiology

Diseases	References
Alopecia[1]	(15,16,33)
Hirsutism, hypetrichosis[1]	(16,33)
Skin wounds[2]	(20,21,29)
Prurigo nodularis	(35)
Psoriasis	(43)
Systemic sclerosis	(44)
Atopic dermatitis[2]	(24,45,46)[3]
Urticaria	(47)
Malignant melanomas	(48)
UV-irradiated skin	(49)

[1]Because NGF-p75^{NTR} and BDNF-TrkB (15,16,33) as well as pro-NGF (16) negatively control hair follicle growth, p75^{NTR} and/or TrkB antagonists might be explored as hair growth-stimulatory drugs for alopecia, while corresponding agonists might be applied for therapy of unwanted hair growth in hirsutism and hypertrichosis (33). Yet, an adipocentric question remains like a sword of Damocles: whether SCAT may produce any hair growth-modulatory factors?
[2]Whilst treatment with NGF accelerates wound healing (21), inhibition of NGF production suppresses pruritus associated with atopic dermatitis (45).
[3]BDNF is also implicated.

Table 3. Adipokines as possible modulators of inflammation

Anti-inflammatory signals	Pro-inflammatory signals
Adiponectin	Tumor necrosis factor-α
Nerve growth factor[1]	TWEAK
Interleukin-10[1]	Leptin
Matallothionein-1, -2[1]	Plasminogen activator inhibitor-1
Interleukin-1 receptor antagonist	FIZZ-1[2], Resistin (FIZZ-3)
Oestrogen[3]	Interleukin-1, -6, -18
Tissue inhibitor of matrix metalloproteinases	Matrix metalloproteinases
Prohibitin	Monocyte chemoattractant protein-1(CCL2)
Adrenomedullin	Interleukin-8 (CXCL8)
Urocortin	Eotaxin (CCL11)
Calcitonin gene-related peptide	RANTES (CCL5)
Transforming growth factor-β1	Oncostatin M

For references, see the text.
[1]NGF may suppress inflammation by increasing IL-10 production (50); for metallothioneins (51), both references dealing with brain inflammation.
[2]Inhibits the neurotrophic action of NGF (52).
[3]Accelerates cutaneous wound healing by stimulating paracrine secretion of NGF, IL-10 and TGF-β1, and attenuates inflammation in psoriatic lesions (29). Again, this intriguing update does not appreciate SCAT. Adipo-promisingly, at an endocrine level, there are data of (i) elevated plasma levels of leptin, TNF-α and adiponectin in patients with systemic lupus erythematosus (53), and (ii) skin wound healing-promoting effect of leptin treatment in *ob/ob* mice (54).

thermore, local application of NGF cures human skin and corneal ulcers (21). Adipocentrically, the stromovascular or matrix fraction of adipose tissue, if seeded over skin wounds, can promote healing (22), suggesting the secretion of adipose-derived wound healing factor(s), of which NGF is one possible candidate. Let it be noted here that early-stage romantic love is associated with elevated NGF plasma levels (23), whereas the purported kissing-induced benefit to the clinical course of atopic dermatitis, interestingly, is accompanied by reduced NGF plasma levels (24). Whether, and if so: which, NGF-related *adipocyte functions* orchestrate these hedonistic epidermal events remains a most intriguing object of future study.

Adipose tissue is now recognized as a potent source of, and important target for, numerous pro-inflammatory (2,6,7,13,25,26) and anti-inflammatory (2,7,8–13,27–29) signals, whose balance between may consequently trigger or inhibit the inflammation in various skin diseases (Table 3). Here, a special comment is required for (i) a pro-inflammatory network, including tumor necrosis factor-alpha (TNF-α) (2,6,7,25), TNF-like weak inducer of apoptosis (TWEAK) (26) and various adipokines of chemokine nature (see Tables 1 and 3), and (ii) an anti-inflammatory network, including adiponectin (2,4,8–10,13), interleukin-10 (IL-10) and IL-1 receptor antagonist (27,28).

Dysregulation of TNF-α has been linked with several skin diseases, such as systemic sclerosis, psoriasis, atopic dermatitis, pyoderma gangrenosum, and keloids (25). Adiponectin, instead, which antagonizes many TNF-α effects (9), reportedly exerts multiple biological benefits, ranging from *anti*-inflammatory, *anti*-atherosclerotic and *anti*-thrombotic via *anti*-obesity and *anti*-diabetic to proposed *anti*-cancer effects (2,4,8,9,30).

The possible significance of such an '*anti*kine' activity in cutaneous health and disease deserves special research attention. Specifically, the paracrine secretory activity of SCAT can no longer be ignored in investigative dermatology. Indeed, we found only two studies in cutaneous research that, at the paracrine level, adopt an 'adipocentric' view of skin biology (20,22). If signals can, *via* endocrine pathway, be targeted from the visceral adipose depot through the bloodstream towards many organs in the body, and hence lead to various metabolic, vascular and inflammatory disorders, then why not look for similar, but paracrine reactions from the SCAT?

Table 4. Immunohistochemistry of neurotrophins and their receptors in subcutaneous adipose tissue

Molecules	Adipocytes	Stroma
NGF	+/–	+++
TrkA	++	+++
BDNF	+/–	+/–
TrkB	+/–	+/–
NT-3	+/–	++
TrkC	+/–	+/–
$p75^{NTR}$	–	–

+++, strong positivity; ++, clear positivity; +, weak positivity; +/–, lack of clear evidence for positivity/scattered single weakly positive cells; –, negative.
Immunohistochemical staining for NGF and BDNF, and their high-affinity receptors, TrkA and TrkB, in human subcutaneous adipose tissue (on the day of still birth). Note that while both NGF and TrkA are localized mainly to the non-adipocyte, stromal compartment, TrkA is expressed also by adipocytes. The BDNF-TrkB system appears to be only weakly expressed.

Thus, studies aimed at evaluation of the molecular composition of SCAT become mandatory, as identification of these molecules (most notably, adipokines), may yield clues to a possible transmission of pathogenic and/or protective stimuli, emanating from SCAT (in the subcutis), but targeting epidermis, dermis, cutaneous vasculature and nerves, and/or skin appendages.

Hence, new subspecialty of investigative dermatology is called for: 'cutaneous adipoparacrinology'. This emerging field now must systematically explore the adipokine–skin connection for increasing our knowledge of, for example, inflammation in skin diseases. Encouraging recent examples of such a paracrine approach include (i) epicardial adipose tissue and cardiovascular disease, (ii) orbital adipose tissue and thyroid-associated ophthalmopathy, (iii) mesenteric adipose tissue and inflammatory bowel disease, and (iv) mammary adipose tissue and breast cancer (2,7,31,32). *Why not* SCAT and skin disease!

Studying without thinking is worthless.
Thinking without studying is dangerous.
Confucius (551–479 BC)

Following Confucius' lesson, let us briefly turn to our own, pilot results related to *adipocyte function*. Among many adipokines, our (and not only Ralf Paus' [15,16,33]) favourite ones are NGF, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and their respective high-affinity receptors, TrkA, TrkB and TrkC. We have examined their immunohistochemical expression in SCAT of newborn rats ($n = 5$) and humans (still birth; $n = 5$), in accordance with the Ethical Board of Medical University, Plovdiv, Bulgaria.

Our findings reveal the presence and distribution of NGF-TrkA and BDNF-TrkB in SCAT, with NGF-TrkA being more prominently expressed than BDNF-TrkB. Table 4 summarizes our results. These provide additional and novel *in situ* evidence in support of the presence of NGF-TrkA, BDNF-TrkB and NT-3-TrkC in SCAT (1,10–12 for NGF in cultured white adipocytes; 17–19 for NGF in brown adipose tissue). As indicated above, data of 'white' NGF expression in wounded skin (20) deserve fuller appreciation, and careful follow-up. We are convinced that this will be neither *worthless* nor *dangerous*.

The submerged areas of the NGF iceberg loom very large.
Rita Levi-Montalcini

Today, a dazzling variety of evidence indicates that 'NGF functions beyond the neurological horizon' (33). Discovered in 1951 as a neurotrophic factor (34), NGF and related molecules (reviewed in 14) are known today to also act as (i) immunotrophins (35), (ii) epitheliotrophins, targeting also keratinocytes (33,36), and (iii) metabotrophins in glucose, lipid and energy homeostasis (13,37). Which of these actions might be exerted by adipose-derived NGF, BDNF and/or NT-3, remains to further be studied in experimental dermatology. One may also wonder whether adipose tissue, rather than submandibular glands (34), is the human's body largest source of NGF (1,2,10–13,17–19).

In summary, we have sketched selected recent concepts and data suggesting that *adipocyte function* matters in cutaneous biology. Furthermore, adipose tissue-derived stem cells can be exploited to differentiate into various cell types, including neural cells and cardiomyocytes (38), thus pointing to exciting new frontiers in regenerative medicine by autologous adult stem cell therapy from an extremely easily accessible source – your own SCAT.

Because 'the enemy of the good is the better' (39), our next essay on this topic, which hopefully will be inspired by new data that you, esteemed reader will have published by then, must offer more concrete details. Thus, we expect to be writing, next, about cutaneous adipopharmacology (see 40), including (adipo)biologics (39), biosimilars, pharmaceuticals and nutraceuticals. Until then, we remain,

Neurotrophically yours,

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Viewpoint 4

For years often neglected as a simple energy store, a thermal and mechanical insulation pad, the adipose tissue only recently has stepped out of obscurity and neglect into the spotlight of interdisciplinary endocrinology. Accordingly, research over the last years – notably performed almost exclusively by non-dermatologic scientists – has begun to highlight another fascinating function of the fat, namely, its role as an endocrine organ.

Indeed, the skin has been well appreciated as a target and producer of many hormone and hormone-like mediators (1). However, most of our current knowledge on the (neuro)endocrine system of the skin is based on studies with non-adipocyte cell types. Therefore, our current picture of the skin as an endocrine organ including the autocrine/paracrine actions of its hormones and hormone-like mediators has been largely concentrated on the epidermis and dermis. Now accumulating evidence exists that adipocytes likewise express multiple receptors for hormones and hormone-like mediators.

For example, murine 3T3-L1 adipocytes were found to express many if not all receptors for pituitary hormones [i.e. the prolactin receptor, melanocortin type 2 receptor (MC-2R), thyroid-stimulating hormone receptor, follicle-stimulating hormone receptor, luteinizing hormone recep-

tor, oxytoxin receptor and the vasopressin receptors 1A, 1B and 2] thereby generating the concept of *adipotropins* (2,3). Moreover, an active role of adipocytes within the general endocrine system has been documented by the capacity of the fat to autonomously produce and actually secrete an increasing number of hormones (with leptin as a withstanding factor) and hormone-like mediators (4,5).

These secreted peptides and proteins have been collectively termed *adipocytokines*, or more appropriately, *adipokines*, as many of the adipocyte-derived factor are clearly not classical cytokines. Of note, expression of a distinct factor by adipocytes does not necessarily mean secretion, and for some of the listed adipokines (Table 1), the term *putative* adipokine may be still more precise (5).

Until now the biological role of hormone receptors expressed by adipocytes and adipokines has been mostly studied within the context of diseases of metabolism, e.g. metabolic syndromes or diabetes mellitus as well as its associated diseases. The fact that adipokines however not only are capable of modulating energy balance, appetite, lipid and glucose metabolism, insulin resistance but also haemostasis, blood pressure, inflammatory and immune responses, angiogenesis and wound healing strongly suggests a more complex role of these substances in cutaneous physiology and pathophysiology. In the next section we will therefore draw attention to some arbitrarily selected adipokines and their putative role within the endocrine/paracrine/autocrine network of the skin.

Table 1. 'Adipokines' expressed/secreted by adipocytes

Type of adipokine[1]	Name
Cytokine	IL-1β
	IL-6
	IL-8
	IL-10
	IL-17D
	IL-18
	MCP-1
	TNF-α
	TGF-β
Hormone	Leptin
	Steroid hormones
	Angiotensinogen
	ASIP
Neuropeptide	NGF
Modulator of lipid glucose metabolism	IGF
	Adiponectin
	Resistin
	CETB
	Perilipin
	Apelin
	Visfatin
	RBP
	LPL
	PPAR-γ
	ZAG
	aP2
Acute phase protein	PAI-1
	Haptoglobulin
	Serum amyloid A
	α_1-acid glycoprotein
	CRP
Other	Monobutyrin
	Metallothionein
	Adipsin
	P450 aromatase

aP2, adipocyte lipid-binding protein; ASIP, agouti signal protein; CRP, C-reactive protein; IGF, insulin-like growth factor; IL, interleukin; HSL, hormone-sensitive lipase; LPL, lipoprotein lipase; MCP, monocyte chemoattractant protein; NGF, nerve growth factor; PAI, plasminogen activator inhibitor; PPAR, peroxisome proliferator-activated receptor; RBP, retinol binding protein; TGF, transforming growth factor; TNF, tumor necrosis factor; ZAG, zinc-α_2-glycoprotein.

[1]Note that some adipokines may be classified into more than one category.

Leptin

The concept of the white adipose tissue as a diffuse endocrine organ has been strongly supported by identification of leptin which is produced from fat cells, enters the circulation, and after reaching the hypothalamus activates corresponding receptors leading to production and release of anorexigenic neurotransmitters and inhibiting orexigenic neuropeptides. Interestingly, regarding the skin it was shown that in the leptin-deficient obese/obese (*ob/ob*) mice systemically and topically applied leptin significantly improved re-epithelialization and restored impaired wound healing (6). The salutary effects of leptin have been also confirmed in excisional skin wounding of normal mice (7). The latter studies further showed that leptin expression in subcutaneous adipocytes (and also in other cutaneous cell types) is upregulated upon skin wounding which is in accordance with increased levels of leptin in wound fluids collected from partial-thickness excisional wounds in pigs (8). The activity of leptin in wound healing is mediated by leptin receptors which are not only expressed in the adipose tissue itself but also in fibroblasts, endothelial cells and keratinocytes. As leptin is a mitogen for keratinocytes and acts as an angiogenic factor this hormone provides compelling evidence for a local endocrine ('tissue-crine' axis) in the skin.

Corticotropin-releasing hormone (CRH)

Until recently, expression and functional characterization of the CRH system of the skin has been studied primarily in non-adipocyte cells. In the skin, CRH is regarded as a key regulator of the stress response orchestrating cellular downstream events such as expression and processing of proopiomelanocortin (POMC), release of POMC-derived peptides

including ACTH and α-melanocyte-stimulating hormone (α-MSH) and corticosteroid biosynthesis in analogy to the hypothalamic-pituitary-adrenal axis (9,10). Expression of the CRH-like peptides urocortin and stresscopin as well as the CRH receptors (CRH-R) 1 and 2 has recently been reported for human adipocytes (11). CRH-R1 appears to be the predominant CRH-R type present in subcutaneous adipocytes as expression of CRH-R2 was lower or even undetectable in subcutaneous fat tissue compared with visceral fat (11,12). Moreover, subcutaneous fat expressed higher levels of the above CRH-like peptides than visceral adipose tissue. In vitro CRH down-regulated CRH-R1 and 2 expression in cultured human adipocytes suggesting a paracrine/autocrine role of the CRH system within the adipose tissue. Given the postulated role of CRH as a cutaneous stress sensor however it is tempting to speculate on an analogous role in subcutaneous tissue, e.g. after trauma or inflammation. On the other hand, given the well-described CRH-R expression by other cell types located in close vicinity of subcutaneous adipocytes (e.g. hair follicle epithelia and sebocytes), it will be intriguing to assess the putative role of adipocyte-derived urocortin and stresscopin in the regulation of adnexal functions in more detail.

Agouti signal protein (ASIP)

This peptide is known as a natural antagonist against the melanocortin-1 receptor (MC-1R) and MC-4R, the former increasing eumelanin synthesis in pigment cells. At present no evidence exists for a physiological role of ASIP in human pigmentation but ASIP is expressed at highest levels in adipose tissue (13). Studies investigating the in vitro effect of the murine homologue of ASIP, agouti protein (AP), on human adipocytes (14), and in vivo studies on transgenic mice with AP overexpressed in adipose tissue (15), support a direct lipogenic effect of ASIP. However, definitive proof for ASIP secretion by adipocytes still awaits confirmation and little is known about the signals that regulate ASP expression in human adipose tissue. If ASIP is secreted by human adipose tissue it may act as an antagonist of MC-Rs which are widely expressed by the majority of cell types of human skin (16). We have recently shown that human dermal papilla cells express both MC-1Rs and MC-4Rs which mediate an anti-inflammatory effect of α-MSH, i.e. downregulation of the intercellular adhesion molecule-1. ASIP significantly abrogated the effect of α-MSH on intracellular cAMP, the key signal transducer activated by this peptide (17). These findings give rise to the provocative speculation that adipose tissue-derived ASIP may antagonize the anti-inflammatory actions of α-MSH within the skin and thereby may also be involved in the pathogenesis of inflammatory skin diseases.

In the light of the above examples, it is apparent that adipokines (via autocrine and paracrine actions) are likely to exert pleiotropic tasks within the entire skin organ – in addition to being secreted into the circulation as hormones and acting only as negative regulators of the release of neuropeptides/neurotransmitters by the brain. Our current paradigm of the skin as an endocrine organ has yet to fully integrate the subcutaneous adipose tissue. Specifically, we need to aim at understanding precisely how the adipose tissue 'talks' with the rest of the skin, and vice versa, and whether and how the complex, bidirectional skin talk with the brain (18) is mediated, at least in part, via subcutaneous adipose tissue.

Thus, deciphering the role of subcutaneous adipocytes as novel players in the endocrine network of the skin represents a cutting edge of cutaneous and general neuroendocrinology.

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Viewpoint 5

What are subcutaneous adipocytes really good for? This is a difficult question made more difficult by the remarkable diversity of subcutaneous adipocytes considering species and location. The answer to this question is highly dependent on which subcutaneous adipocytes are considered or which adipocytes are considered truly subcutaneous.

Subcutaneous adipocytes are identified as such in many species and are widely distributed under the skin in most species. However, rat inguinal adipocytes are considered subcutaneous although they only lie under the skin in a very discrete area. In the porcine species and man, adipocytes are present in several layers of subcutaneous tissue (1–10). In the porcine species there are three layers of subcutaneous adipose tissue that are distinguished from each other based on a number of traits (1–4). For instance, adipocyte size and number and the expansion or growth of subcutaneous layers are very 'layer' dependent in growing swine (1,2,4). Based on measures of lipolysis and lipogenesis, adipocytes in the middle (larger) subcutaneous layer are metabolically more active than outer layer adipocytes (1,2,4,11). Ultrasonic techniques have been used to study all three subcutaneous adipose tissue layers over time in individual swine (3,4). Such studies have shown that genetic obesity and level of feed intake influence subcutaneous adipocyte growth in a markedly layer-dependent manner (3,4). For example, the level of feed intake primarily influenced the growth or accretion of the middle subcutaneous layer but did not influence growth of the inner layer in swine (3). In man, two layers of subcutaneous adipose tissue, i.e. deep and superficial layers in the abdominal region, have been identified and studied (5–10). The deep subcutaneous layer is comparable to the porcine middle layer and is also metabolically more active than the superficial layer (9). Furthermore, the deep subcutaneous layer has a much stronger relationship to insulin resistance than the superficial subcutaneous layer (5,6).

Does the existence of subcutaneous adipose tissue layers per se imply different roles or functions? Do adipocytes in the outermost layer serve more as a protective covering, an insulator or shock absorber than do adipocytes in the inner layers? Conversely, are adipocytes in the middle subcutaneous layer more involved in metabolic homoestasis than are adipocytes in the outermost layer? Or, as our fetal studies have shown, do developmental traits provide evidence to explain functional differences in subcutaneous adipocytes?

Studies of developing subcutaneous adipose tissue in the porcine fetus indicate that layers of sparsely vascular subcutaneous tissue are clearly evident before adipogenesis (12,13). Remarkably, despite little fetal adipogenesis, patterns of middle and outer subcutaneous tissue thickness in the fetus are identical to patterns of middle and outer subcutaneous adipose tissue thickness in growing and adult swine (caudal to cranial and dorsal to ventral). Furthermore, development of the vasculature and associated adipogenesis in fetal subcutaneous tissues proceeds along a ventral to dorsal gradient, i.e., through the middle layer to the outer layer (Fig. 1; 12,13). Therefore, do developmental gradients indicate that it is just a matter of blood flow that makes subcutaneous adipocyte layers different in regard to adipocyte size, lipogenesis and lipolysis?

In addition to the functional distinction of subcutaneous adipocytes from different layers, there is significant divergence in subcutaneous adipocyte characteristics or function even within a layer (1,14–17). In swine, outer layer subcutaneous adipocytes located in distal locations are less lipogenic than outer layer subcutaneous adipocytes in more proximal locations (1). In man, distal and proximal subcutaneous adipocytes respond differentially to weight loss and account for serum leptin levels to different degrees (15,16). Furthermore, non-insulin dependent diabetes mellitus is associated with an increase in more proximal (upper trunk) subcutaneous adipose tissue accretion in men and women (17,18) and a decrease in distal (lower leg) subcutaneous adipose tissue accretion in women (17).

A most remarkable example of variation within the subcutaneous layer was demonstrated in a study of adipose tissue blood flow following an oral glucose challenge (14). At a constant depth and only a 16–20 cm difference between anterior abdominal wall subcutaneous sites, there were significant site differences in blood flow changes following oral glucose administration (14). Collectively, these findings indicate that there can be significant differences in the

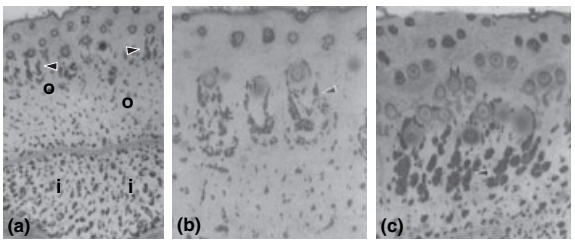

Figure 1. Lipid-stained sections of subcutaneous adipose tissue from 105 day control (a, b) pig fetuses and a 105 day pig fetus from an obese and feral dam (c). The outer layer (o), inner layer (i) and adipocytes located around hair follicles (arrowheads) are shown in (a). Note the enhanced development of both hair follicles (hf) and hair follicle adipocytes (arrowhead) in a fetus from an obese and feral dam (c) compared with a fetus from a control lean dam (b).

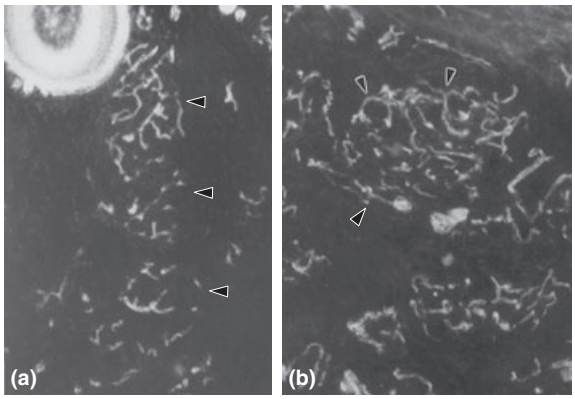

Figure 2. Sections of subcutaneous adipose tissue from 105 day control (a, b) pig fetuses stained to delineate only blood vessels (arrowheads). Note the hair follicle in top left of (a). Note the distinction between middle layer adipocytes (b, arrowheads) and adipocytes located around hair follicles (a, arrowheads) based solely on blood vessel anatomy.

function of subcutaneous adipocytes within the same layer (14).

In a final but poignant example of why it is so important to contemplate which subcutaneous adipocytes exactly are considered, or which adipocytes are truly subcutaneous, we must consider our studies of 'hair follicle' adipocytes in swine (Figs 1 and 2; 19–23). Adipocytes located around hair follicles in swine are anatomically and developmentally distinct from other adipocytes in the outer subcutaneous layer (Figs 1 and 2; 19–23). Several lines of evidence demonstrate that the development of hair follicle adipocytes and hair follicles is tightly coupled temporally and spatially and regulated by the thyroid hormones (19–23). For instance, hair follicle (hair) and hair follicle adipocyte development was markedly enhanced by thyroxine treatment of both hypophysectomized and intact swine fetuses (21,22). After just 5 days of thyroxine treatment hair follicle adipocyte development was increased 23-fold in contrast to a less than onefold increase in adipocyte development in the outer and middle subcutaneous layers (22). Furthermore, thyroxine treatment increases hair follicle development two to threefold in hypophysectomized and intact swine fetuses (21,22). Swine fetuses from obese and feral dams have elevated levels of thyroid hormones associated with enhanced development of both hair follicles and hair follicle adipocytes when compared with fetuses from control dams (20; Fig. 1b,c). We also discovered a close developmental relationship between hair follicles and hair follicle-associated adipocytes in young rats (24). Apparently, in man, adipocytes are only similarly grouped around hair follicles in the scalp.

Collectively, our studies have led us to suggest that adipocytes distinctly located around hair follicles may be a functional component of hair follicles and skin. In this regard, it is very clear that hair follicle adipocytes may be more involved in thermogenesis than other subcutaneous adipocytes. Furthermore, hair follicle adipocytes may provide a 'base of operations' for hair follicles as they progress through hair growth cycles thereby potentiating or allowing hetereogenous hair growth cycles evident in man. Therefore, it appears that hair follicle adipocytes represent subcutaneous adipocytes that are good for hair follicles in not one but two important ways.

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Viewpoint 6

Anatomy of subcutaneous adipose tissue

For centuries, human subcutaneous adipose tissue (SAT) has been the victim of blatant discrimination by anatomists and their illustrators. Musculature, lymphatics and blood vasculature are always displayed with the adipose tissue removed (1), creating the impression that it is unimportant. Nonetheless, transgenic mice lacking adipose tissue demonstrate its many central roles in metabolism (2).

As a comparative anatomist, I regret reaching the conclusion that early comparative studies, especially those of John Hunter (1728–1793) and George Stubbs (1724–1806), have encouraged disregard of human SAT. In most lean terrestrial mammals, SAT is localized to a few sites, notably inguinal, axillary and sometimes on the outer abdominal, though in natural and artificially induced obesity, these depots thicken and spread laterally, merging to form an almost continuous layer of SAT. At least near their origins, the depots retain many of their site-specific properties (3), making SAT inhomogenous.

Extensive adipose tissue on (as well as in) the abdomen is a consistent feature of primates (4,5). This depot and hypertrophy of the intra-abdominal depots, especially the omentum, are the main bases of the protruding belly that is so characteristic of older humans and great apes. For reasons that remain poorly understood, SAT is thickest on the lower abdomen in women, yet on the upper abdomen (extending onto the sternal region) in men. The proportions and postures of human arms and legs spread SAT over a large area and bring more of some internal depots into contact with the skin.

An example of the latter is the popliteal depot that surrounds the popliteal lymph nodes behind the knee (Fig. 1). In typical mammals with crouching posture of the hind legs, most of this depot is intermuscular, with only a narrow strip at the back of the thigh being 'subcutaneous'. But in humans with fully extended knees, the popliteal depot spreads over the gastrocnemius muscle of the calf and between the semitendinosus and semimembranosus of the lower thigh (6). The thighs and upper arms are relatively longer in humans (and most other primates) and their excursion at the hips and shoulders is greater than in most mammals. The SAT around these limbs, which originates as axillary and inguinal, is therefore spread under a larger area of skin. Human SAT retains the site-specific properties found in other terrestrial mammals (6) but observations on patients suffering from lipodystrophy (absence of most or all SAT) show that it remains distinct from structural adipose tissue and usually from intra-abdominal depots (7).

Functions of subcutaneous adipose tissue

Insulation and thermoregulation.

Except in specialized marine groups (Cetacea, Pinnipedia and Sirenia), the partitioning of adipose tissue between superficial and internal depots in wild mammals is not consistent with the hypothesis of specialization for thermal insulation (8). Humans are no exception. The brain generates so much heat and is so severely impaired by deviations from its optimum temperature that humans frequently risk overheating. Improved dissipation of heat at the body surface was among the principal, if not the sole, factor promoting the evolution of reduced body hair (9). Readily adjustable, sometimes very high, rates of blood flow through the skin further improve thermoregulation (10). The replacement of pale skin and dark hair (as found in other great apes) with darkly pigmented, almost hairless skin occurred early in hominid evolution and enabled extensive cutaneous synthesis of vitamin D (11).

Recent reports of paracrine interactions between adipocytes and blood vessels (12,13) suggest that more extensive and elaborate vasculature could itself promote the formation of SAT. The anatomical consequences of these adaptations to thermoregulation are that the skin and superficial adipose tissue become more visible (14). Humans are social animals who use binocular and colour vision more than smell, and readily assess emotion, health (e.g. pallor and blushing) and sexual and social status from body conformation and the colour and texture of the skin and hair.

Protection and immunity.

Understanding of the relationship between adipose tissue and the lymphatic and blood vessels has long been undermined by the well-meaning but misguided efforts of scientific illustrators to represent 'physiological systems' (1). The neat, thorough dissection shown in Fig. 1a is the basis for innumerable textbook drawings of lymph nodes and vessels; the adipose tissue that in life invariably encases these important structures (Fig. 1b), even in naturally very lean mammals (Fig. 1c), remains secret – except to observers of the tissues in situ.

A few months after his death, we acknowledge the insight of the Swedish scientist, physician, poet, novelist, administrator and political activist Lars Gyllensten (1921–2006) who concluded from the histology of developing lymph nodes in guinea-pigs (15) that: 'there may be presumed to be an interaction between fatty tissue and lymph nodes'. Recent investigations reveal the predicted paracrine interactions between adipose and lymphoid cells

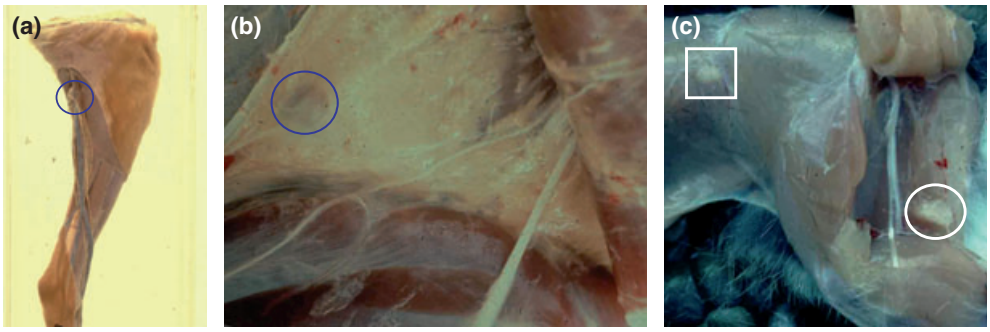

Figure 1. Representations of the relationship between adipose tissue and the immune system. (a) The popliteal 'space' in the right hind leg of a dog, dissected to show the popliteal lymph node (blue ring) and associated lymph and blood vessels (specimen in The Hunterian Museum, The Royal College of Surgeons, London). (b) The popliteal lymph node (blue ring) embedded in adipose tissue, gastrocnemius muscle, sciatic nerve and saphenous vein of the right leg of a healthy wild polar bear (*Ursus maritimus*), in situ with the skin removed and the biceps femoris muscle reflected dorsally. (c) The skinned left-hand side of the posterior body of a healthy wild rabbit (*Oryctolagus cuniculus*) with popliteal (ringed) and inguinal (rectangle) perinodal adipose tissue, showing the popliteal (ringed) and inguinal (rectangle) perinodal adipose tissue *in situ*.

(16,17). Adipocytes adjacent to lymphoid structures supply fatty acids and possibly other necessary precursors to the immune system within hours of its activation, thereby emancipating local, transient immune responses from competition with other tissues (e.g. liver, muscles) for essential nutrients or disrupting whole-body lipid metabolism.

Human skin is thin relative to body size, even compared to mammals such as domestic pigs that are almost hairless, kept mostly indoors, and exposed to minimal abrasion and other mechanical damage. Our skin is more vulnerable to blood-sucking insects, infections, UV light and mechanical damage than that of most other mammals. The skin's inflammatory response to all these insults includes the synthesis and secretion of prostaglandins and leukotrienes (18), with the keratinocytes themselves making a major contribution (19). In vitro studies show that fatty acids are important determinants of keratinocyte properties (20). Whether these specialized epidermal cells have sufficient reserves of the necessary fatty acid precursors to support prolonged inflammation, and whether supplies are supplemented by paracrine acquisition of fatty acids from SAT, remain to be established.

Leptin, among the most thoroughly studied of all adipocyte secretions, promotes healing of cutaneous (21) and vascular (22) wounds, though excess can be detrimental. Human subcutaneous adipocytes secrete more leptin than omental adipocytes (23); their role, especially when abnormally numerous, in supporting skin healing remains to be elucidated.

Human SAT is infiltrated with various immune cells (24). Although they can form lymphomas (25) and in certain pathologies can become so numerous that they surround the adipocytes (26), in healthy people, they are probably not numerous enough to be easily studied in standard biopsies and would be unlikely to survive destructive techniques such as liposuction. Animal studies show that dendritic cells harvested from lymph nodes or from the perinodal adipose tissue itself modulate lipolysis in adjacent adipocytes (27).

Figure 2 compares adipocytes anatomically associated with lymph nodes with those remote from visible lymphoid structures; there may be adipocytes specialized to such paracrine interaction around smaller lymphoid structures but in laboratory animals, lymph vessels are too small to dissect out. Some lymphologists believe that perilymphatic adipocytes have a central role in the lymphatic system including that of SAT (28–30).

Adipocytes specialized to interact locally with immune cells (see Fig. 2) contribute less than 'standard' adipocytes to whole-body lipid supply during prolonged fasting, even though in vitro studies demonstrate their supranormal response to noradrenaline (31). These paracrine interactions, like those of blood vessels, may promote the formation of more adipose tissue (32), though it is important to note that areas of skin most exposed to injury, the feet, hands, forearms and head, have little or no SAT. These effects cannot account for more than a thin layer of SAT; paracrine involvement with even major lymphoid structures such as lymph nodes extends only 5–10 mm into the surrounding adipose tissue (16).

This paracrine role of SAT has evolved alongside that of determining body conformation and skin texture. Smooth, clear skin, especially on the face, breasts, abdomen and hips, is a universal marker of youth, health and general sexual attractiveness, while scars, warts, pustules, boils, lipoatrophy and wrinkles convey the opposite message. SAT may promote skin attractiveness mechanically, by improving its appearance and tactile properties, and by supporting immune processes that avert infections and enable fast, efficient healing. The social role of skin and SAT texture may

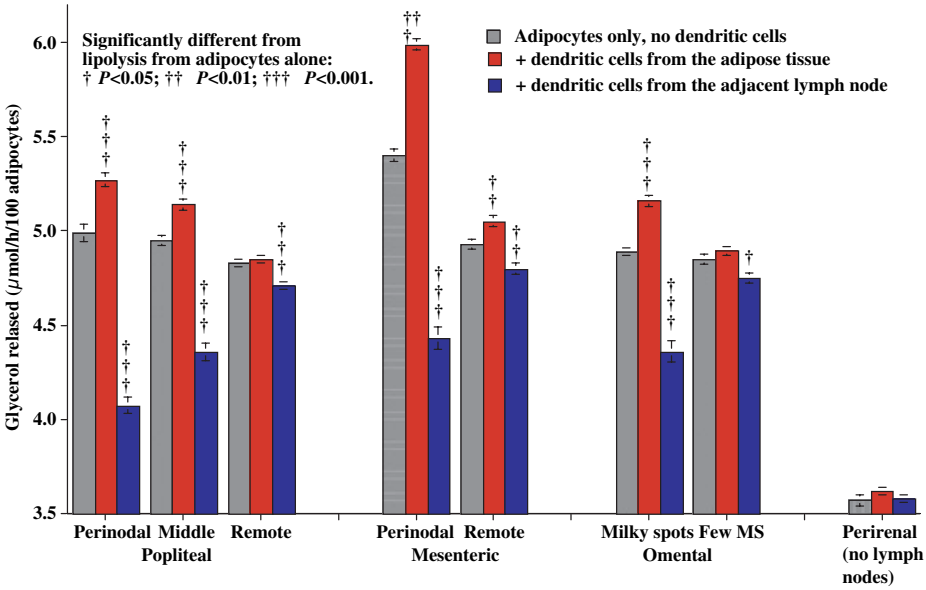

Figure 2. Control of lipolysis by dendritic cells in adipocytes from three adipose depots of adult rats associated with lymphoid structures and perirenal (a large nodeless intra-abdominal depot). Lipolysis over 3 h in the presence of 10^{-5} M noradrenaline from collagenase-isolated adipocytes from three popliteal, two mesenteric and two omental sites defined by their anatomical relations to lymphoid structures, and perirenal. Grey bars: control, without dendritic cells; red/grey bars: with about 2000 dendritic cells that originated from the same adipose tissue as the adipocytes; blue bars: with about 2000 dendritic cells collected from the adjacent lymph nodes (or the region of the omentum rich in milky spots); injected with 20 μg lipopolysaccharide in both hind legs thrice a week for the final 2 weeks. $n = 24$ adult male rats. Differences between control without dendritic cells and with dendritic cells by Student's *t*-test: †significant at $P < 0.05$; ††significant at $P < 0.01$; †††significant at $P < 0.001$.Data from Mattacks et al. (27).

be emphasized by scarification, tattooing and other forms of body decoration (33).

Energy storage.

This most widely recognized role for SAT is deliberately mentioned last. In wild mammals and birds, this tissue is replete and therefore extensive only during periods (e.g. just before migration, hibernation or reproductive fasts) when they are fatter than normal: the superficial depots fill up more slowly and are depleted sooner than internal depots.

The opposite situation, selective hypertrophy of intra-abdominal adipose tissue, is all too common in modern people and is linked to metabolic disorders (e.g. type II diabetes) (34,35) that are not found in naturally obese wild mammals. Comparative studies show that Western people, even those of 'normal' body mass, are fatter than almost all wild mammals, so it is not surprising that SAT is often extensive and thick even in people with large intra-abdominal depots.

Direct measurements in vivo show that human SAT makes a major, probably predominant, contribution to stabilizing fatty acid levels in the blood (36). Extensive lipodystrophy is associated with several metabolic disorders (7). Some experts believe that adipose tissue, including SAT, may prevent more than promote the many metabolic disorders arising from prolonged, severe obesity (37–39).

The expression of certain control genes with increasing fatness differs in superficial and intra-abdominal adipose tissue (40) but how they produce the inter-individual differences in the thickness and extent of SAT remains to be established. The roles of inflammatory processes (41–43) and leptin (22) in human obesity are now widely discussed. Prolonged inflammation can induce adipocytes to develop properties typical of perinodal adipocytes (44). If these inflammation-induced changes included resistance to the endocrine signals of fasting (see Fig. 2), the adipose tissue would become refractory to slimming.

How far hypertrophy of SAT facilitates or impedes its other functions remains to be determined; possible mechanisms are already being discussed (45–47). Insufficient wound healing and various chronic dermatological conditions, not all of which can be attributed to the mechanical consequences of excess adipose tissue, are much commoner among the obese (48), as are many infectious skin diseases (49).

In conclusion, SAT has several indispensable roles – but as so often in physiology, too much of a good thing may prove harmful.

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Viewpoint 7

We argue that adipocytes in the subcutis are there for the best, the bad and the worse!

Not too much, not too little

The ideal feminine silhouette has evolved with the rhythm of culture (Fig. 1). The goddesses of antiquity were carrying a significant layer of subcutaneous fat. This was also observed in thighs and hips of women up to the Renaissance. This energy reserve was considered as an asset assisting in surviving periods of starvation. The ideal of a thick layer of subcutaneous fat progressively vanished, up to the modern lean models. Average is the best as subcutaneous fat is a typical female sexual trait. Its excess or defect is a cause for concern. Without this regular layer that smoothen their shapes as observed in lipodystrophies, the female patients acquire a cachectic face and a male aspect of their body contour with apparent veins and muscle masses (Fig. 1d). AIDS patients treated with combined antiretroviral drugs also suffer a similar distressing aspect accompanied by central adiposity (1).

Adipocytes and connective tissue

Adipocytes are not different from any other cells associated in organs in that they need a support with which they exchange information. The so-called 'cellulite' and its orange peel aspect is mostly apparent in the gynoïd lipodystrophy. It might be related to a sex-linked architecture of the deep dermal fat lobules and the organization of the connective tissue septum of the hypodermis, as proposed by Nürnberger and Müller (2), although this concept is not completely supported by recent magnetic resonance imaging data (3).

Alteration in the connective tissue septum of the subcutaneous tissue is a main cause of the aspect of aged skin and the so-called gravitational folds (4). The adipocytes remodel their supporting connective tissue to extend it

upon lipid storage. Upon reduction of the size of the adipocytes, the connective tissue is irreversibly laxed by the loss of mechanical (and endocrine) control (5). Grafting fat pad from non-affected skin locations in classical partial lipodystrophies or AIDS patients is most often of inconsistent benefit by rapid resorption (6). This perhaps also results from the lack of adequate cell–cell control of the adipocytes and its associated connective tissue support (7).

Useful functions

Besides their energy storage capacity, subcutaneous adipocytes provide a mechanical protection to the underlying structures. They also potentially participate in many other functions by their multipotentiality in terms of differentiation and secretory activity. Cells that mature into different lineages (neurones, myocytes and adipocytes and others) have been described in skin (8) and in the subcutis (9). Neonatal mouse skin adipocytes express stem cell antigen 1 (Sca 1) (10), further supporting the concept that the subcutis is a stem cell repository.

Figure 1. Evolution of the subcutaneous adipose layer with time and fashion: upper left, statute of Aphroditis, right painting of P.P. Rubens, below left a famous model of the present time and below right the destressing aspect of a lady presenting a classical acquired partial lipodistrophy.

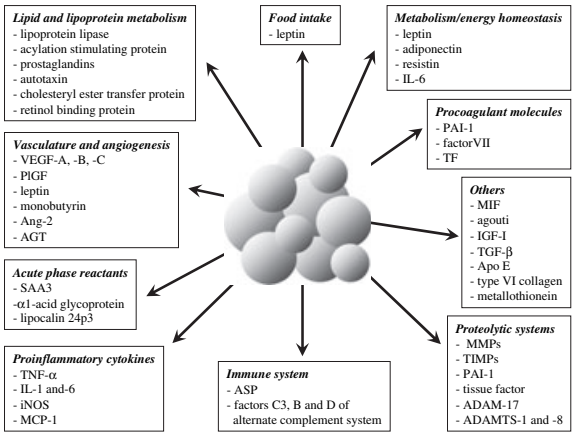

Figure 2. Overview of the major functions modulated by adipocyte-derived factors. ADAM, a disintegrin and metalloprotease; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; AGT, angiotensinogen; Ang-2, angiopoietin-2; Apo E, apolipoprotein E; ASP, acylation stimulating protein; IGF-I, insulin-like growth factor-I; IL, interleukin; iNOS, inducible nitric oxide synthase; MCP-1, monocyte chemotractant protein-1; MIF, macrophage migration inhibitory factor; MMP, matrix metalloprotease; PAI-1, plasminogen activator inhibitor-1; PlGF, placenta growth factor; SAA3, serum amyloid A3; TF, tissue factor; TGF-β, transforming growth factor-β; TIMP, tissue inhibitor of MMP; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor [adapted from Lafontan (23)].

Adipocytes are not identical in all locations (11). Furthermore subcutaneous adipose tissue is not homogeneous as it contains white and brown adipocytes, at least up to the neonatal period (12). In view of the plasticity of adipocytes in culture one can envision that they participate in various physiological and pathological processes, e.g. by secretion of the adipokines that they produce (13), which include proangiogenic factors (14; Figure 2).

Adipocytes also collaborate in tissue repair, as suggested by their promotion of epidermal regeneration in vitro (15). In the healing wound, a high number of actively dividing hypodermal cells observed rapidly after trauma (16) might be derived from the subcutaneous adipocytes or their precursors. The abundance of the Sca1+ cells in fetal skin still needs to be considered in the context of scar-free type of healing in the foetus.

During the anagen phase of the hair follicle cycle, the increased size of the subcutis (17,18) may provide a dynamic, supportive environment for maintenance of the metabolically highly active, maximally proliferating anagen hair follicle. Interestingly the secreted 'agouti' protein (which regulates hair pigmentation, e.g. in mice) is also involved in adipocyte regulation (19). Agouti is physiologically expressed in skin, and this mainly during the anagen phase of the hair cycle (20).

Adipocytes as a 'secretory factory'

In addition to fatty acids and other lipid moieties, adipocytes synthesize a host of adipokines involved in a plethora of autocrine, paracrine and endocrine functions. In subcutaneous adipose tissue, approximately 20% of its known genes encode secreted proteins (21). The diversity of these factors includes, among others, enzymes, cytokines, growth factors and hormones (12,22–27). Some of these proteins play a role in lipid metabolism, some are inflammatory cytokines, while others are involved in vascular haemostasis, extracellular matrix remodelling or the complement system (Fig. 2).

Adipocytes and the metabolic syndrome

Recent observations suggest that increased oxidative stress in accumulated fat, via increased NADPH oxidase and decreased antioxidant enzyme activity, causes dysregulated production of adipokines such as PAI-1, tumor necrosis factor-α (TNF-α), resistin, leptin and adiponectin. These participate in the pathogenesis of obesity-associated metabolic syndrome. Increased production of PAI-1 and TNF-α from accumulated fat contribute to the development of thrombosis and insulin resistance respectively. In contrast, adiponectin exerts insulin-sensitizing and anti-atherogenic effects, and hence a decrease in plasma adiponectin contributes to insulin resistance and atherosclerosis in obesity. Increased reactive oxygen species production from accumulated fat also leads to increased oxidative stress in blood, affecting other organs including the liver, skeletal muscle and aorta, suggesting that increased oxidative stress in accumulated fat represents an early instigator of obesity-associated metabolic syndrome.

A current paradigm stipulates that subcutaneous fat plays a minor role in the development of the metabolic syndrome (28,29). However, new pieces of evidence demonstrating that the subcutaneous fat, by acting as a metabolic sink, protects against the metabolic syndrome of obesity, challenge this concept (30,31).

Adipocytes and cancer

The mesenchymal cells normally present in connective tissues include several cell types, most notably fibroblasts, endothelial cells and adipocytes. It is becoming increasingly clear that these cells actively participate in tumor development (32,33). The existence of critical cross-talks between cancer cells and adipocytes is emerging (34,35). Owing to their capacity to secrete adipokines, adipocytes are excellent candidates to influence tumor behaviour through heterotypic signalling processes, which prove to be critical for tumor survival, angiogenesis, growth and metastasis (36,37).

For example, breast cancer cells exhibit differential response to leptin and adiponectin, two major products of subcutaneous adipocytes: leptin stimulates while adiponectin inhibits tumor cell proliferation (38,39). Moreover, both epidemiology and experimental observations suggest that obesity-associated dysregulation of adipokines is likely to contribute significantly to the pathogenesis of several cancers (40). Accelerated tumor formation in fatless (A-ZIP/F-1) mice with type 2 diabetes and inflammation, however, seems to contradict this paradigm (41).

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