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).

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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?

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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-

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