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Opinion

Dermal Adipocytes: From Irrelevance to Metabolic Targets?

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Dermal white adipose tissue (dWAT) has received little appreciation in the past as a distinct entity from the better recognized subcutaneous white adipose tissue (sWAT). However, recent work has established dWAT as an important contributor to a multitude of processes, including immune response, wound healing and scarring, hair follicle (HF) growth, and thermoregulation. Unique metabolic contributions have also been attributed to dWAT, at least in part due to its thermic insulation properties and response to cold exposure. Dermal adipocytes can also undergo an adipocyte–myofibroblast transition (AMT), a process that is suspected to have an important role in several pathophysiological processes within the skin. Here, we discuss emerging concepts regarding dWAT physiology and its significance to a variety of cellular processes.

Dermal Adipose Tissue: A New Depot with New Properties

Over the past few years, adipose tissue morphed from a passive tissue with well-known functions, such as energy storage, mechanical protection, and heat insulation, to a systemically relevant, physiological player with many different features. It transformed from an initial quasi-static structure to a slowly renewing tissue with characteristic half-lives of embedded adipocytes of approximately 10 years [1]. Subsequently, adipocytes were discovered to be involved in highly dynamic events, such as HF cycling [2], and in even more rapidly acting processes, such as wound healing [3]. The concept of the common white adipocyte in contrast to that of the classical brown adipocyte was expanded to the 'beige' adipocyte, blurring the lines between the two classical extremes; 'beige' adipocytes are emerging as a new class of 'chimeric' adipocytes that can simultaneously display properties of both adipocyte subtypes. Even more complex are the events leading to the differentiation of these types of adipocytes *in vivo*, in terms of differences in specific fat pads and developmental stages and the precursor cells that are recruited and activated [4]. At the same time, the description of sWAT was changed from it being a homogeneous to a highly heterogeneous structure with a broad, body area-dependent distribution of adipocyte sizes [5] and variable mechanical and electrical properties primarily determined by its peri- and intercellular fibrotic structures [6–10]. There is widespread belief that we must abandon the simple concept of the adipocyte as a uniform cell type, exerting comparable functions independent of its location.

The introduction of a new adipose tissue depot, which we refer to as dWAT [11,12], is a logical consequence of this development. This depot in humans has a geometry uniquely distinct from all other known fat depots and demonstrates intriguing spatial correlation with hypertrophic scarring (see Figure IC in Box 1). Adipocytes from this unique depot within the dermis are involved in various physiological and pathological processes, including HF cycling [2], wound healing [3], cutaneous fibrosis [13], skin aging [14], homeostatic temperature regulation [15], and protection against skin infection [16].

Trends

Dermal adipocytes are a population of cells that are distinct from subcutaneous adipocytes. Unlike other fat depots, these cells demonstrate high phenotypic flexibility and high turnover rates.

Their ability to undergo AMT suggests that they are involved in scarring.

Dermal adipocytes exhibit insulating action, and are involved in hormonal skin reactions, as well as HF growth.

dWAT can have antimicrobial peptides and, thus, is involved in the pathogenesis of some skin efflorescences.

dWAT can be spatially inhomogeneous, thus contributing to the mosaic structure of the skin and being involved in skin hyperpigmentation.

dWAT is emerging as a critical metabolic tissue that can also be considered a new target in antiscarring, antiaging, and hair regrowth strategies.

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Box 1. Special Geometry of dWAT in Humans

Whereas anatomically dWAT can be classified as a separate adipose tissue depot, in humans it has a special geometry uniquely distinct from all other known fat depots. It has long been appreciated that two histologically and anatomically distinct layers of adipose tissue exist under the reticular dermis. This anatomical difference is evident in rodents, where the layers are separated by the panniculus carnosus, a layer of striated muscle cells (Figure IA,B).

In human skin, where all layers in the dermis have interfaces that run more or less parallel to the skin surface, dWAT is mainly concentrated around the pilosebaceous units that contain hair shafts, HFs, sebaceous glands, and erector pili muscles, and the dWAT has a special cone geometry [52] (Figure IC). Each dermal cone has two parts: the upper part is placed in the dermis and the lower part (referred to as the 'fat dome') transverses the dermis and penetrates the sWAT [53]. Thus, single dWAT units build the vertical fractional structures that are connected with each other through the interfollicular dermis and have a common reservoir of adipocytes in sWAT. Such geometry can sufficiently influence the metabolic properties and functions of dWAT in humans, especially since the individual units can interact with each other through paracrine signaling, producing characteristically sized clusters of cells.

Analysis of skin histology in humans reveals that the cone structures in the dermis are present only in those body areas where hypertrophic scars can be produced (e.g., cheek, neck, chest, abdomen, back, buttock, arm, forearm, dorsal hand, thigh, leg, etc.) and are not apparent in body areas that are less prone to scarring (e.g., in early fetus, palm, scalp, forehead, etc.). Also, animals with a more limited propensity for scarring after wounding (such as rats and rabbits) have a reduced number of these structures. Whereas morphological characteristics of dWAT (e.g., cell size distribution) have not been investigated in depth, the existence of these regional correlations between scarring and dWAT means that dWAT structures and content are different in distinct body areas, which in turn is reflected in the spatially variable pathways involved in wound healing, hair growth and cutaneous fibrosis in these areas.

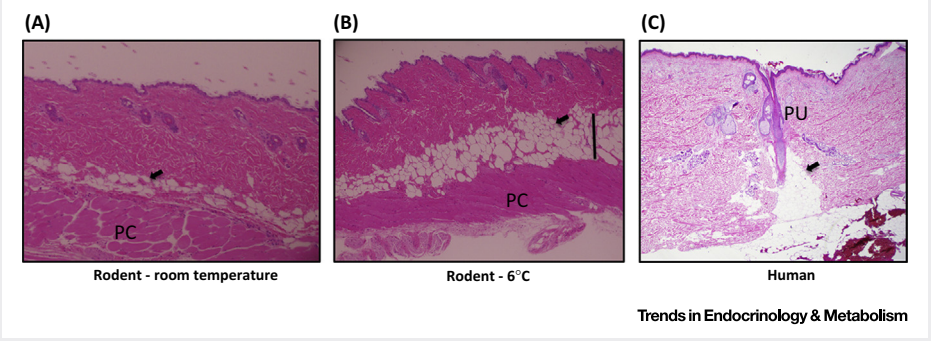

Figure I. Typical Layered Dermal White Adipose Tissue (dWAT) Structures in Rodents and Humans. (A) Section of dWAT from a C57/Bl6 mouse maintained at room temperature. The dWAT contains several layers of adipocytes (arrowheads) placed parallel to the panniculus carnosus (PC). (B) Section of dWAT from a C57/Bl6 mouse after cold exposure to 6°C for 4 days; both hypertrophy and hyperplasia can be seen (area indicated with a black line). dWAT can quickly react to different types of physical and pharmacological stimulus with significant modulation of its thickness. (C) Human adipocytes congregated around the single pilosebaceous units (PU) producing the 'dermal cones' (arrowhead). Morphological characteristics of these cones are dependent on the body area and phase of the hair follicle cycle. Reproduced, with permission, from Min Kim (A,B) and Travis Vandergriff (C).

Whereas dWAT has been talked about in various settings in the literature during the past few years, many important questions remain (see Outstanding Questions). Among them are the possible phenotypic differences between dermal adipocytes and the adipocytes from the underlying sWAT. This is important in the context of the unique extracellular matrix (ECM) microenvironment in which these cells are embedded. This also raises the question of how this ECM drives the expression of unique dWAT phenotypes in terms of their local spatial and global metabolic phenotypes as well as the role of these cells in inflammation and scarring.

dWAT and Myofibroblasts: Are They Independent Global Contributors to Wound Healing and Scarring?

If dWAT is involved in the wound-healing process [3], one can suppose that dermal adipocytes are somehow connected with scarring. The appearance of myofibroblasts in injured tissue is

connected with their differentiation from the existing pool of fibroblasts or with the epithelial to mesenchymal transdifferentiation of epithelial cells. This differentiation was long believed to be an irreversible process. According to this model, the only way to remove low-motility myofibroblasts from the tissue to avoid scarring seemed to be their death through apoptosis. Therefore, defective apoptosis of myofibroblasts was thought to be the main reason for fibrosis and scarring [17], and major efforts were undertaken to understand the nature and possible pathways for the regulation of this process. More recent data argue that this model needs to be revised. First, myofibroblasts are not terminally differentiated cells, and they have a phenotype with a high degree of plasticity (i.e., they can either re- or dedifferentiate [18,19] into other cell types). Second, while the dysfunctional regulation of apoptosis of the myofibroblasts may still have an important role, it is far from being the only reason for scarring upon skin wounding. For example, under excessive scarring conditions, such as the development of keloids, myofibroblasts completely disappear after the granulation phase and are not present in mature scars. Third, adipose tissue is directly involved in the activation of fibroblasts in the wound [3]. Fourth, myofibroblasts can emerge from adipose-derived intradermal progenitors; moreover, an entirely new pathway, the AMT, can significantly contribute to fibrosis [13]. This puts the spotlight in the context of wound healing and scarring on adipogenic progenitors and mature adipocytes, an important novel role beyond the direct metabolic role for these cells.

The Versatile Dermal Adipocyte: Immature and Mature Adipocytes in Wound Healing and Scarring

As in every adipose depot, dWAT contains adipose-derived stem cells (ADSCs), preadipocytes, and mature adipocytes, which can be differentially involved in the above-mentioned processes. Mature dermal adipocytes repopulate the skin wound, and this process is realized via activation of adipogenic precursors and adipogenesis [3]. These cells appear in the wound concurrently with fibroblasts. This suggests a possible crosstalk between these two cell types. At the same time, wounds in lipoatrophic mouse models, such as A-ZIP/F1 mice, which lack mature white adipocytes system-wide and only carry immature adipocyte precursor cells, demonstrate aberrant recruitment of fibroblasts and wound instability [3]. The same is true for mice treated with inhibitors of the master adipogenic factor peroxisome proliferator-activated receptor gamma (PPARγ). Blocking PPARγ produces defective, immature adipocytes, and the absence of functional adipocytes again has a negative impact on wound healing. By contrast, immature adipocytes are not only necessary, but also sufficient for the proper HF cycling [2], given that almost normal HF cycling is observed in A-ZIP/F1 mice.

Whereas the role of ADSCs in tissue regeneration was intensively investigated during the recent years [20], we are far from having a clear picture of their involvement in this process. A recent report indicated that ADSCs can differentiate into myofibroblasts or fibroblast-like cells using growth factors present in the wound bed. In this context, transforming growth factor beta (TGFβ) can stimulate the myofibroblastic phenotype, whereas basic fibroblast growth factor (bFGF) reduces this conversion [18]. Remarkably, these authors also demonstrated that myofibroblasts can redifferentiate into fibroblast-like cells, which could be an important mechanism for ensuring that these cells disappear without the need to undergo apoptosis from a wound whose healing process has fully resolved. Application of ADSCs can modulate the processes of early scar formation and remodeling, and improvements in scar formation were shown to correlate with suppression of TGFβ and enhanced expression of matrix metalloproteinases [21]. Altogether, the role of myofibroblasts in hypertrophic scarring might be overestimated in current models, whereas the role of immature dermal adipocytes is underestimated (Box 2).

The Transition from the Adipocyte to a Mesenchymal Cell

In a recent paper, Varga and colleagues demonstrated that myofibroblasts can be produced from the adiponectin-positive intradermal progenitors (i.e., these cells are derived from dermal

Box 2. The Pathophysiology of Hypertrophic Scars: Mesenchymal Stem Cells or Myofibroblasts?

One important marker for myofibroblasts is ∝ smooth muscle actin (∝SMA). High expression of ∝SMA in correlation with wound contraction was assumed to be a sign of the presence of fat-derived (myo)fibroblastic cells in the healing wound, since fibroblast-like cells isolated from subcutaneous fat contain a high percentage of (∝SMA)-positive cells [54]. However, ∝SMA is also a well-known mesenchymal stem cell marker. Therefore, it is possible that the adipose-derived cells previously described as myofibroblasts are in fact ADSCs. Indeed, cultured mesenchymal stem cells from sWAT and from hypertrophic scars demonstrate significantly higher expression of ∝SMA than the corresponding stem cells taken from dermis [54]. Such expression correlates with higher production of collagen I and collagen cross-linking in these cultures. This leads to a model in which ADSCs are responsible for hypertrophic scar formation. In a tissue-engineered human scar model, ADSCs isolated from healthy human skin (in contrast to dermal mesenchymal cells) indeed facilitated hypertrophic scar formation [55].

adipocytes) [13]. A well-characterized model of dermal fibrosis involves the administration of daily subcutaneous bleomycin injections for 2 weeks. This leads to a progressive increase in dermal thickness and collagen deposition, ultimately leading to dermal fibrosis. This is associated with marked attenuation of the intradermal adipose layer [22]. Remarkably, the loss of intradermal adipocytes after bleomycin treatment could not be explained solely by intradermal apoptosis. The authors proposed that dermal fibrosis might appear through transdifferentiation of dermal adipocytes. Recently, Martins and colleagues [23] reported that resistin-like molecule alpha (RELM∝/FIZZ1) can cause the suppression of adipocyte-specific genes, leading to dedifferentiation, while simultaneously inducing ∝-smooth muscle actin (∝SMA) and type I collagen expression, reflecting a transition to myofibroblasts. RELM∝ is induced in the bleomycin-induced dermal fibrosis model also used by Varga and colleagues. These observations were further supported by additional *ex vivo* studies on adipocytes. Whereas ADSCs cultivated for 10 days differentiated into typical adipocytes, application of TGFβ produced an unusually rapid modulation of cell morphology. After 24 h, these cells were in a transition state and expressed both perilipin and ∝SMA. Later, they lost the adipogenic markers altogether and further increased ∝SMA, producing the typical features of myofibroblasts [13]. AMT could be of primary importance for cutaneous fibrogenesis. This has additional implications in the context of adipose tissue loss that frequently correlates with fibrosis in lipodystrophy secondary to panniculitis, different autoimmune diseases, and cancer cachexia, as well as under other conditions (Box 3), and suggests that this phenomenon is of general physiological importance.

There are a host of additional factors that may be critical for the process of fibrosis locally. Connective tissue growth factor (CTGF; also known as CCN2) can induce human bone marrow mesenchymal stem/stromal cells (MSCs) to differentiate into fibroblasts. More importantly, CTGF expression levels are correlated with the amount of peri-adipocyte fibrosis in WAT from obese individuals [24], but it is not known whether CTGF has a role locally in dWAT.

Box 3. Adipocytes in the Involution Processes

Another process that is physiologically important is the restructuring of the mammary fat pad during lactation. During late pregnancy and postpartum, many adipocytes in the mammary gland disappear as the milk-producing lobules appear and then reappear during involution of the milk-producing structures. The mammary fat pad is considered a subcutaneous fat pad (sWAT). The involution process remains an incompletely understood process. Cinti and colleagues suggested a transition from adipocytes to epithelial cells as a possible mechanism [25]; recently, the same was assumed to also be important in fat grafting [56]. Another possibility is that adipocytes simply undergo apoptosis. A third possibility is that they undergo AMT and turn into fibroblasts. Clearly, there is a limited understanding of this process, and much work needs to be done to determine the fate of these mammary adipocytes.

Similarly, during breast cancer progression, there is a significant reduction in the number of adipocytes in the mammary gland as the transformed ductal epithelial cells break through the basal lamina and invade the stromal compartment. In this situation, it will be important to determine whether the adipocytes simply apoptose, or whether there is a conversion going on resembling AMT, with the resulting fibroblasts potentially having a direct role in tumor progression. A recent paper by Seo and colleagues [57] highlighted the role of these myofibroblasts, which are more prominent in obese adipose tissue, for the tumor growth-promoting enhanced ECM in this context. With the availability of newer models, such as the 'adipochaser' mouse [58,59], it should be straightforward to determine the fate of adipocytes in these settings.

Both the adipo-epithelial transition [25] and AMT [13] must have important roles in physiological and pathophysiological processes in the skin involving dWAT. For example, processes of epithelial–mesenchymal remodeling are strongly involved in the cycling of HFs, being especially pronounced during mid-anagen (the active growth phase of HFs) at the distal end of growing follicles [26]. This correlates with the disappearance of dermal adipocytes during mid-anagen and the massive production of these cells during the late-anagen subphase of the HF cycle [2], when epithelial–mesenchymal remodeling processes are strongly suppressed. By contrast, AMT can be involved in the formation of so-called 'connective tissue streamers', which are residual fibrovascular tracks representing the transient, lower part of the HF [27]. These tracks are normally developed during the involution phase of the HF cycle and can be considered as local microscarring in the site of HF involution.

Are Dermal Adipocytes 'Chimeras'?

Recently, Cinti and colleagues suggested the existence of cells with an intermediate adipo-epithelial phenotype in the mammary gland during and after pregnancy [28]. However, this does need to be independently validated. The same phenomenon must be the case for adipocytes from dWAT, which have much higher turnover rates than are typical for sWAT. These transformations in dWAT occur over a short time frame, compared with the HF cycle or even with the characteristic times of wound healing. This reflects a higher propensity of dermal adipocytes to undergo these transitions, likely reflecting transcriptional machinery that is highly responsive to environmental changes. Although we cannot conclude unambiguously from these data that dermal adipocytes are more flexible in their phenotypic adaptations than adipocytes from sWAT, such enhanced flexibility is strongly suspected.

Fetal Skin and Oral Mucosa Do Not Form Scars: A Reflection of the Absence of dWAT?

Every theory of cutaneous scarring must be able to explain the scarless wound healing in oral mucosa and fetal skin (at least during the first trimester of development) [29,30]. This property has long been considered to be mainly connected to the special structure and dynamics of the ECM in these tissues, which significantly deviates from the situation in adult skin. However, the introduction of adipocytes as new global players in wound healing and scarring demands the reanalysis of these phenomena, which must take into account the adipogenic features of fetal skin and oral mucosa.

Adipose tissue in the fetus appears and progressively develops from the 14th to 24th week of gestation (i.e., during the second trimester of fetal development [31]), whereas HFs appear at around 10 weeks' gestation. Interestingly, it was recently shown that development of dWAT in the mouse occurs independently of sWAT and must be primarily connected with the appearance of HFs [32]. If the AMT [13] is involved in dermal scarring by wound healing, this process must be completely excluded during the first trimester of gestation, thereby explaining the lack of scar formation during the healing process in the early fetus. By contrast, mucosa (other areas that do not form scars at any stage of development or in the adult) do not contain any intradermal fat tissue. Instead, mucosa contain the lamina propria, a thin layer of loose connective tissue that lies beneath the epithelium and, together with the epithelium, constitutes the mucosa. Thus, the scarless wound healing in oral mucosa also correlates with the absence of dermal adipocytes in this tissue.

Mosaic Skin Structure: Is There a Link to dWAT Clusters That Has Gone Unnoticed?

Different physical characteristics of the skin point to its fractional microstructure. The spatially inhomogeneous distribution of skin properties (nicely reflected in the mosaic structure of dermal electrical conductivity, for example) can be at least partly correlated to the fractional structure of

dWAT in humans. One example is observed in HF cycling. In humans, the phases of the hair cycle are believed to be independent of neighboring HFs, thus producing the spatially random HF structure; by contrast, rodents clearly demonstrate spatially coordinated HF growth. Taking into account the essential role of dWAT in HF cycling [2], it might be that this phenomenon is connected with the fractional dWAT structure in humans versus the continuous nature of dWAT in rodents. At the same time, a characteristic correlation radius of a single dWAT unit in humans should be dependent on the interfollicular distance and, thus, one can expect some spatial correlation between HFs at least for small interfollicular intervals. Another phenomenon connected with fractional dWAT structure might be skin hyperpigmentation (Box 4).

To our knowledge, this is the first published discussion of the idea of clustering and spatial correlation of processes in dWAT units. Such clustering is also untypical for sWAT. If such clustering units indeed have a functional role, they will have an impact on not only physiological, but also pathological processes in the skin and might even impact superficial sWAT layers.

Is dWAT Metabolically Relevant?

dWAT depots in rodents and in humans have different structures. Our insights into the metabolic properties of dWAT stem predominantly from studies in rodents. Since we lack specific markers for dWAT, there are no genetic tools to selectively manipulate this depot. However, insights have been gained from several different knockout mouse models. One of these is the caveolin 1-knockout mouse, wherein the dWAT layer is completely absent [33]. Caveolin-1 is an important signaling mediator that is highly abundant in adipocytes, and has a complex metabolic role system-wide in many different tissues [34]. Deficiency of caveolin-1 leads to increased cell death and fibrosis of sWAT [35]. Another model is the syndecan 1-null mouse, which has a profoundly depleted dWAT layer [15], showing that syndecan 1 is also essential for adipocyte differentiation [15,36]. The third model is the Collagen VI-knockout mouse, which demonstrates significantly increased dWAT [6]. Collagen VI is essential for the terminal differentiation of preadipocytes [37]; its absence improves the metabolic phenotype of the mice, in part at least due to the reduced fibrosis prevalent in normal adipose tissue upon exposure to high-fat diets [6]. It appears as though dWAT and sWAT in the Collagen VI-knockout model demonstrate opposite responses, with the subcutaneous layer potentially being thinner in contrast to the hypertrophic nature of the dWAT. However, selective overexpression of endotrophin (a cleavage product of the collagen VIα3 chain) in adipocytes, also leads to adipose tissue fibrosis and massive hyperproliferation of the dWAT layer [38], suggesting that dWAT is highly responsive to either increases or decreases in the local fibrotic microenvironment.

While the main focus of these models was the characterization of conventional adipose tissue depots, the skin modifications in these knockout models were not investigated in depth. Only in

Box 4. Is Skin Hyperpigmentation Connected with dWAT?

In skin hyperpigmentation (e.g., melasma), irregular but well-demarcated hyperpigmented macules randomly appear over a large surface area. Pathogenesis of melasma has been long connected with a local stimulation of melanocytes placed in the epidermis, but now there is increasing evidence that other cells have a key role in this process [60]. To influence the melanocytes, these cells must be located in the vicinity of the epidermis and their activity must be spatially inhomogeneous, which could mediate the fractional structure of hyperpigmentation. One possible candidate for this might be dWAT units grouped into clusters that have a characteristic radius and that mediate the effects on melanocytes through paracrine signaling. Indeed, ADSCs were shown to suppress melanin production both *in vitro* [61] and *in vivo* by intradermal injections [62]. Proposed mechanisms include the secretion of TGFβ1 by ADSCs, which provides significant inhibition of melanin synthesis through downregulation of tyrosinase and expression of tyrosinase-related protein 1 (TRP1). In addition, TGFβ1 is a well-known dominant paracrine mediator that determines HA and collagen expression profiles [63]. Another group recently confirmed this effect and proposed that inhibition of melanin synthesis can be realized via interleukin 6 [64]. From this point of view, the fractional structure of skin hyperpigmentation can be theoretically connected with the local absence of ADSC paracrine activity.

the syndecan 1-null mice did the authors suggest an important role of dWAT in homeostatic thermoregulation, which includes involution and expansion of the dWAT layer in response to changes in ambient temperature [15]. This example demonstrates that dWAT can respond to other cues and in different ways compared with sWAT. Whereas sWAT normally responds to mild cold exposure with the release of free fatty acids and the induction of browning and/or beiging of WAT, dWAT reacts to mild cold exposure with significant expansion of its thickness (up to fourfold) [15]. This effect is reversible at least in the range of physiological temperatures. Furthermore, this process reaches a maximum response and 'saturation' (i.e., it does not progress towards further expansion with further temperature reduction). The authors suggest that the disruption of the intradermal adipose tissue development could result in cold stress and associated complex metabolic changes. Theoretical modeling of thermal conductivity reported in [15] showed that heat loss through a 40-μm intradermal fat layer (typical for syndecan 1-null mice) must be 1.8-times higher than the corresponding loss through a 200-μm fat layer typical of wild-type mice. Given these data, this is indeed an attractive hypothesis, although difficult to prove directly, given that the layer overall is very thin (a thickness of only five to ten adipocytes).

Another metabolic effect of dWAT is connected with hyaluronan (HA), which is abundantly present in the dermis and provides a distinct ECM structure that is different from that in sWAT. A possible role of HA in conferring resistance of adipocytes to lipolytic stimuli was discussed in [39]. Multiple applications of a hyaluronidase leading to a reduction in local HA content in C57BL/6J mice fed a high-fat diet resulted in a significant (up to 35%) reduction of fat mass with simultaneous reduction of the size of the adipocytes [40]. These results were recently confirmed in [41], which also demonstrated inhibition of adipogenesis in 3T3-L1 cells after downregulation of HA levels *in vitro*. Although neither of these efforts focused on intradermal adipocytes, we can assume similarities with the modifications of dWAT observed in collagen VI-knockout mouse, since purified hyaluronidase is also able to disrupt collagen VI fibers [42].

These examples suggest that dWAT and sWAT not only have different structures, but also react differently to extrinsic manipulations.

Dermal Adipocytes and Hormonal Effects in the Skin: Correlation or Causation?

Since dWAT is potently involved in wound healing and HF cycling, we infer an interplay of dermal adipocytes with androgens, on which there is a longstanding separate literature. There is a pronounced sexual dimorphism apparent with respect dWAT: intact female mice have thicker dWAT than male mice [43]. After gonadectomy, dWAT thickness increased in both male and female mice, whereas treatment with dihydrotestosterone caused its reduction [43], which could be related to an inhibition of adipocyte differentiation [44]. Reduction of dWAT in this study correlated with inhibition of HF growth, thereby further supporting an important role of dWAT in HF cycling [2].

Another relevant hormone in this context is thyroid hormone (TH). TH is a key regulator of the basic metabolic rate [45]. It can induce uncoupling protein 1 (UCP1) expression in WAT via TH receptor (TR)-β [46], highlighting its ability to induce the 'beiging' process in white adipocytes. However, TH is also a strong regulator of adipogenesis and can be involved in both the proliferation and differentiation of preadipocytes [47]. This raises the question of whether some known effects of TH on the skin (e.g., increase in dermal thickness reported both after topical and intraperitoneal TH administration [48]) are connected with dWAT.

Therefore, we assume that at least some established hormonal effects on the skin might be mediated not directly through fibroblasts and keratinocytes, but indirectly through dWAT modulation.

Dermal Adipocytes in Skin Protection: Should We Talk about Skin Efflorescences?

Recent observations suggest that dermal adipocytes are critically involved in the protection of skin against infections [16]. Infection of murine skin with *Staphylococcus aureus* caused a significant expansion of dWAT and induced high-level production of cathelicidin (an antimicrobial peptide) by dermal adipocytes. Moreover, lipodystrophic mice with impaired adipogenesis demonstrated a reduced immune reaction against this pathogen. These results suggest an unexpected link between dermal adipocytes and skin efflorescences.

Cathelicidin is known to be strongly overexpressed in rosacea [49]. Expression of cathelicidin was also shown to be significantly disturbed in atopic dermatitis (AD) and psoriasis [50]. Recently, it was also proposed that antimicrobial peptides are critically involved in the pathogenesis of acne [51]. Since cathelicidin exerts proinflammatory effects [49], overexpression of this peptide leads to a local skin inflammation. By contrast, low-level expression of cathelicidin (as a result of a weak or complete absence of a dWAT response) can be related to a suppressed immune response in the skin.

If dermal adipocytes in humans produce antimicrobial peptides comparable to the observations in mice, it might be that human dWAT is involved in the development of at least some skin efflorescences.

Concluding Remarks

Until relatively recently, the dWAT layer had received minimal research attention. In fact, there has been significant confusion as to how to refer to this fat pad, because dermal and intradermal versus subcutaneous fat tissue were considered synonymous. Most of the phenotypic characterizations of rodent models do not analyze this layer of adipocytes as a distinct entity and, in fact, our own research efforts in the past frequently neglected the description of dWAT. However, there is an emerging picture in the literature that suggests that changes in dWAT have major significance for a variety of processes, and there should be an increasing appreciation of these adipocytes as highly flexible cell types that, despite their 'terminal' differentiation phenotype, may have the potential to undergo delipidation and transitions to fibroblast and myofibroblast-like phenotypes. Future phenotyping efforts should make the examination of dWAT an integral part of the analysis. With more information available about how this layer of adipocytes responds to the genetic manipulations of other fat pads, a better picture may emerge about this interesting structure.

Outstanding Questions

Several questions remain before we can gain a better understanding of dWAT. Specifically, these relate to the communalities and differences between the adipocytes in dWAT and in the adjacent sWAT.

Do dWAT adipocytes arise from identical precursor cells as seen with sWAT adipocytes and do they acquire their distinct characteristics as a function of their unique microenvironment?

Do mature adipocytes in dWAT versus sWAT depots truly reflect functionally distinct cells with unique transcriptional profiles?

Can dWAT adipocytes undergo 'beiging' to the same extent as their sWAT counterparts? There are several interesting correlations, but are these cells truly indispensable for immune responses, HF growth, wound healing, and thermal regulation?

These questions await the availability of genetic tools to selectively manipulate these adipocytes. In the meantime, the identification of unique markers for these cells will facilitate further study of specific adipocyte depots.

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