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Opinion

Dermal Adipocytes: From Irrelevance to Metabolic Targets?

Ilja L. Kruglikov[1] and Philipp E. Scherer[2,*]

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.

[1]Scientific Department, Wellcomet GmbH, Karlsruhe, Germany
[2]Touchstone Diabetes Center, Departments of Internal Medicine and Cell Biology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA

*Correspondence: philipp.scherer@utsouthwestern.edu (P.E. Scherer).

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.

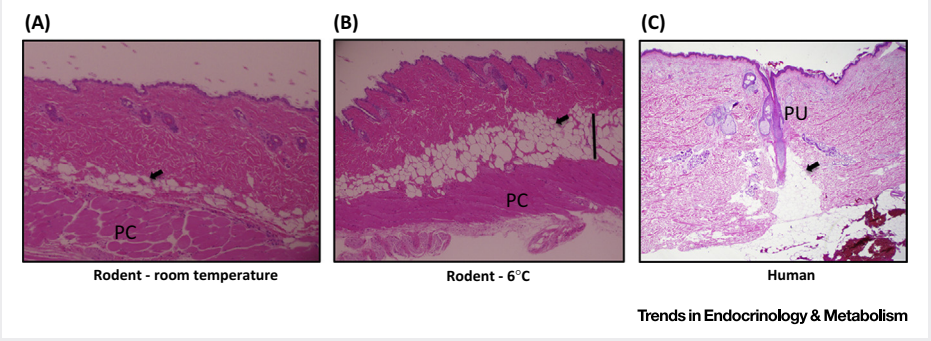

Figure I. Typical Layered Dermal White Adipose Tissue (dWAT) Structures in Rodents and Humans. (A) Section of dWAT from a C57/Bl6 mouse maintained at room temperature. The dWAT contains several layers of adipocytes (arrowheads) placed parallel to the panniculus carnosus (PC). (B) Section of dWAT from 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