Dermal White Adipose Tissue: A Newly Recognized Layer of Skin Innate Defense

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Dermal white adipose tissue is a unique layer of adipocytes within the reticular dermis of the skin. Recently, several nonmetabolic activities have been discovered for dWAT and its fibroblast precursors. These functions include antimicrobial defense and roles in hair cycling, wound healing, and thermogenesis. In this review, we discuss recent progress in understanding the role of dermal white adipose tissue in immunity, both as an innate antimicrobial cell type and as an indirect communicator with other cutaneous immunocytes to enhance defense and potentially contribute to inflammatory disease.

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INTRODUCTION

The skin is a critical barrier that defends against a relentless barrage of pathogens and insults. It has recently been recognized that adipocytes in the dermis provide essential functions that contribute to skin barrier integrity. This layer of adipocytes is known as dermal white adipose tissue (dWAT) to distinguish it from other fat deposits with alternative functions. dWAT participates in thermogenesis (Alexander et al., 2015; Kasza et al., 2014), hair cycling (Festa et al., 2011; Kruglikov and Scherer, 2016a; Schmidt and Horsley, 2012), wound healing (Plikus et al., 2017; Schmidt and Horsley, 2013), fibrosis and scarring (Marangoni et al., 2015; Plikus et al., 2017), and, most recently, immune defense against infection (Zhang et al., 2015; Zhang et al., 2019).

Adipose tissue has been seen as a spacer material involved in energy storage, thermal insulation, and mechanical support (Zwick et al., 2018). However, in general, systemic fat accumulation is associated with negative metabolic and cardiovascular outcomes and cosmetic undesirability (Oikonomou and Antoniades, 2019). Current research shows that adipose tissue is a responsive endocrine organ capable of exerting both local and systemic metabolic and immune effects (Kershaw and Flier, 2004). Not only does adipose tissue contain nearly every immune cell type (Mraz and Haluzik, 2014), but even the adipocyte, its main constituent cell, is capable of producing adipokines and antimicrobial peptides (Schäffler et al., 2010; Zhang et al., 2015). In this review, we highlight the important role of adipocytes in maintaining skin function, with a focus on the immune functions of dWAT.

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Abbreviation: dWAT, dermal white adipose tissue

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THE ANATOMY OF WHITE ADIPOSE TISSUE

White adipose tissue is diverse

Not all adipose depots are alike. White adipose tissue carries out the traditional adipocyte functions of energy storage and metabolism, and brown adipose tissue is rich in mitochondria and functions primarily in heat generation (Avram et al., 2005). Brown adipose tissue arises from $Myf5^{+}$ precursor cells that may also produce skeletal muscle, whereas white adipose tissue develops predominantly from $Myf5^{-}$ precursors (Atit et al., 2006; Sgaier et al., 2005). There are, however, certain depots of white adipose tissue that arise from $Myf5^{+}$ lineage cells, including interscapular and axillary fat, retroperitoneal fat, and inguinal and perigonadal fat, which highlights differences among regional adipose depots in the same organism (Rodeheffer et al., 2008).

Adipose tissue is organized into distinct depots throughout the body that have evolved to perform unique, location-specific functions (Figure 1). For instance, mammary adipose tissue expands and involutes during lactation, whereas epicardial white adipocyte tissue feeds free fatty acids to adjacent myocardial cells (Zwick et al., 2018). Even metabolic syndrome has been clarified as depot dependent: insulin resistance and dyslipidemia can be attributed to visceral fat, but subcutaneous fat has been shown to be protective (Porter and Massaro, 2009). Adipocytes in the skin are no exception to this location-function coupling. dWAT performs functions unique to the skin such as antimicrobial defense, hair cycle regulation, wound healing, and temperature regulation,

Clear differences between fat depots exist at the cellular level. Visceral adipose tissue, which includes omental and organ-encasing fat, has a greater effect on insulin sensitivity and is composed of more immune cells and larger adipocytes compared with subcutaneous adipose tissue (Chengyi et al., 2012). Adipocyte precursor cells (APCs) harvested from these sites behave differently too: adipocyte precursor cells from subcutaneous fat differentiate easily into adipocytes in culture, whereas adipocyte precursor cells from visceral fat differentiate poorly and require bone morphogenetic protein 2 or 4 (Macotela et al., 2012). The developmental timing and gene expression signature of each depot are also variable (Rivera-Gonzalez et al., 2014). These differences between various adipose depots indicate that adipocytes, the functional units of adipose tissue, are different from one anatomic area to another.

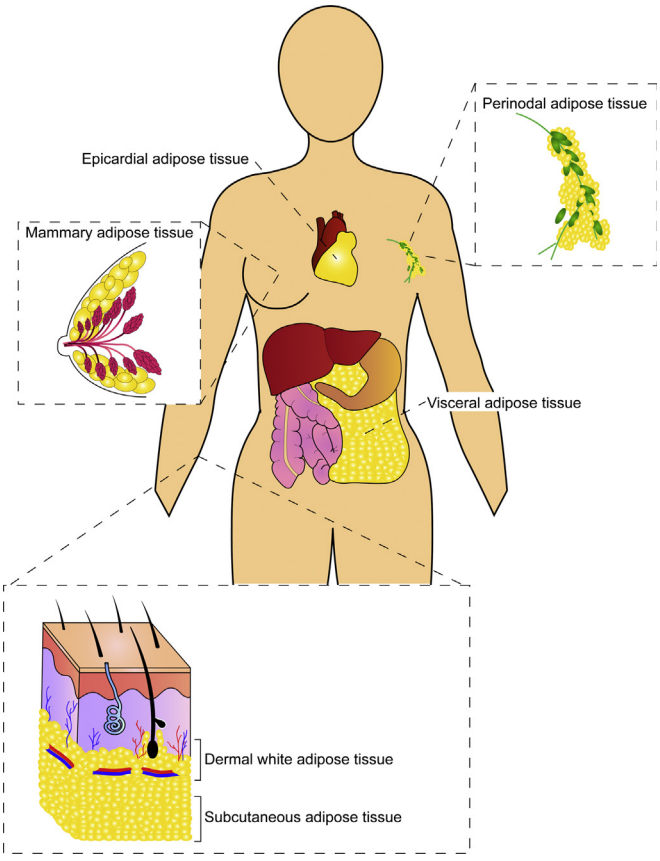

Figure 1. The diverse distribution of white adipose tissue. There are several white adipose depots distributed throughout the human body that include, but are not limited to, dermal adipose tissue, epicardial adipose tissue, perinodal adipose tissue, mammary adipose tissue, subcutaneous adipose tissue, and visceral adipose tissue.

Major cell types in adipose tissue

The notion that adipose tissue functions simply as a spacer material with energy-storing capacities is outdated. It is endocrinologically and immunologically active (Mraz and Haluzik, 2014). Adipocytes are the major cell type in adipose tissue and are derived from mesenchymal fibroblast precursor cells known as *preadipocytes*. Immune cells are the second most common cell type, and nearly all immune cell types are included (Mraz and Haluzik, 2014). Adipose-immune cell balance is essential for maintaining metabolic function. Excess fat accumulation in obesity and concomitant insulin resistance are associated with changes in immune cell number and function, particularly increases in type 1 macrophages and T cells. Similarly, immune cells have a reciprocal effect on adipocytes. The insulin resistance that occurs as a part of normal aging is associated with accumulation of fat-resident regulatory T cells and can be ameliorated by inhibition of these immune cells (Bapat et al., 2015).

Anatomy of dermal white adipose tissue

Skin-associated adipose tissue includes dermal and subcutaneous adipocytes. In mice, these two layers develop independently and are separated by a distinct muscle layer known as the *panniculus carnosus*. The dWAT layer, which is 2–15 cells thick, develops independently from subcutaneous adipose tissue and carries out unique, nonmetabolic functions not observed in subcutaneous adipose tissue (Alexander et al., 2015; Wojciechowicz et al., 2013). In pigs, three adipose layers exist below the skin that each differ in function, development, fatty acid composition, and growth rates (Anderson and Kauffman, 1973). The more superficial porcine adipose layer arises from perifollicular stromal cells and is thought to serve in thermoregulation, and the deeper layers, arising from mesenchyme, function metabolically (Anderson and Kauffman, 1973). Although there is clear evidence of developmentally and functionally distinct adipose layers in many mammals, including rodents, pigs, and bats (Guerrero-Juarez and Plikus, 2018), the existence of a dWAT layer in humans is difficult to confirm given the obvious inability to conduct lineage-tracing studies in humans. However, over the past two decades, increasing evidence has mounted for differentiation between the superficial and deeper parts of subcutaneous adipose tissue (Cappellano et al., 2018; Kosaka et al., 2016; Smith et al., 2001; Walker et al., 2007). In the human abdomen, the sizes of superficial and deep subcutaneous adipose tissue correlate with fasting insulin levels (Smith et al., 2001), and deep subcutaneous adipocytes have a gene expression profile more similar to that of visceral adipose tissue (Walker et al., 2007). A muscle layer analogous to the panniculus carnosus does exist as a vestigial remnant in certain areas of the human body: in the hand (as the palmaris brevis), neck (as the platysma), nipple (as the subareolar muscle), rectum (as the corrugator cutis ani), and scrotum (as the dartos muscle) (McMinn, 2003). In the dermis, adipocytes are concentrated in a conical arrangement around pilosebeaceous units, with the wider aspect of the cone extending inferiorly into subcutaneous white adipose tissue (Kruglikov and Scherer, 2016b). Comparison of various human skin samples showed that these perifollicular, intradermal cones are distributed in areas capable of hypertrophic scarring (such as the cheek, neck, chest, abdomen, buttock) and less so in areas with low scarring potential (palm, early fetal skin, and scalp), suggesting that dWAT in humans could contribute to scarring and fibrosis as it does in mouse skin (Kruglikov and Scherer, 2016b). The current view is that the dWAT layer in humans comprises adipocytes in the reticular dermis (which are primarily perifollicular) and superior hypodermis. Although dermal and subcutaneous adipose tissue are not physically demarcated in humans, they are likely functionally distinct and have been clearly shown to be developmentally disparate in other mammals. Because this distinction has been appreciated only recently, prior studies on subcutaneous adipose tissue may have partly included dermal adipose tissue.

Mature adipocytes are derived from preadipocytes, which are mesenchymal fibroblasts committed to the adipocyte lineage (Figure 2a) that can be identified by surface cell markers (Chia et al., 2016; Rivera-Gonzalez et al., 2014). Adipogenesis is marked by preadipocyte proliferation followed by cell cycle arrest and increased expression of PPAR-γ and CEBP-α. Differentiating preadipocytes develop cellular machinery for lipid synthesis and accumulate lipid droplets. The final mature adipocyte contains unilocular or large lipid droplets and produces specialized, hormonally active biopeptides known as *adipokines* (Avram et al., 2007; Rivera-Gonzalez et al., 2014).

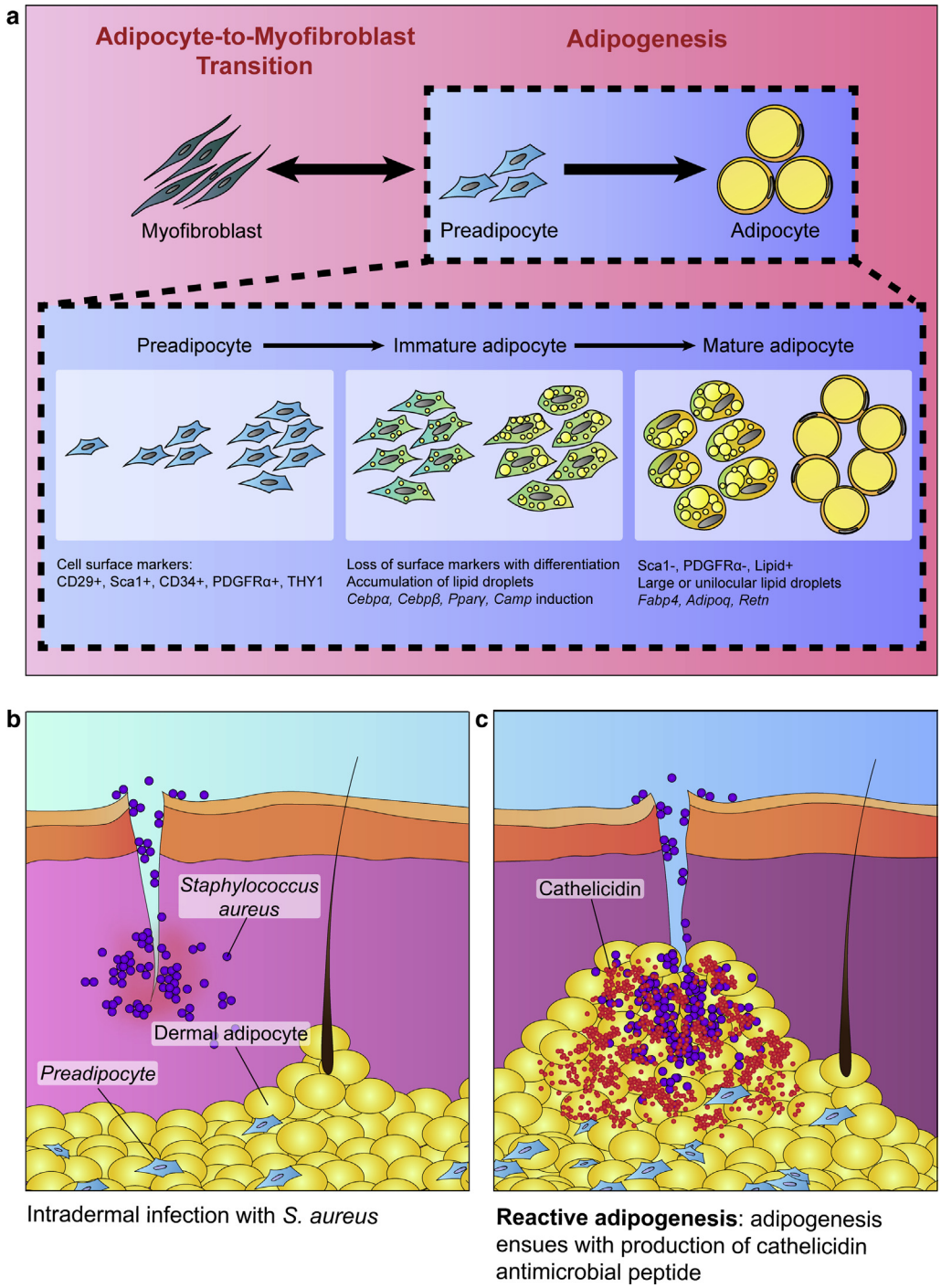

Figure 2. Preadipocytes can undergo reactive adipogenesis and adipocyte-to-myofibroblast transition. (**a**) Preadipocytes may differentiate into lipid-containing cells known as *adipocytes* via adipogenesis or differentiate into myofibroblasts through the adipocyte-to-myofibroblast transition. During adipogenesis, preadipocytes lose their cell surface markers and acquire lipid-synthesizing machinery through induction of CEBP-α/β and PPAR-γ. (**b** and **c**) Reactive adipogenesis occurs in response to *Staphylococcus aureus* intradermal infection. This involves the proliferation and differentiation of preadipocytes into adipocytes, leading to a rapid expansion of the dermal white adipose tissue layer. It is thought that this expansion is triggered to produce cathelicidin antimicrobial peptide, which is produced by immature adipocytes early in differentiation. Adipogenesis-mediated cathelicidin antimicrobial peptide production has been shown as necessary for defense against *S. aureus*.

THE ROLE OF ADIPOCYTES IN THE IMMUNE RESPONSE

The inflammatory potential of adipocytes

Adipocytes display a variety of pattern recognition receptors and adaptor proteins for sensing and responding to bacterial antigens, including TLR1−9 (with higher expression of TLR2, TLR3, and TLR4) (Brenner et al., 2012; Lin et al., 2000; Yu et al., 2014), MDA5 (Yu et al., 2014), RIG-I (Yu et al., 2014), NOD1-2 on preadipocytes (Stroh et al., 2008), MyD88, Mal, and TRIF (Brenner et al., 2012; Poulain-Godefroy et al., 2010; Schäffler et al., 2007). Adipocytes also display chemokine receptors such as IL-1R1 (Caër et al., 2017), IL-17RA (Caër et al., 2017), TNF-R1 (Cawthorn and

Sethi, 2008), and IL-10Rα (Rajbhandari et al., 2018) that produce downstream inflammatory signals. Adipocytes produce several inflammatory cytokines and chemokines, most notably IL-6, IL-8, and MCP-1 (Coppack, 2001; Fain, 2006). In lipopolysaccharide-induced systemic inflammation in mice, visceral white adipose tissue was found to be the major source of IL-6 (Starr et al., 2009).

Adipocytes also produce molecules termed *adipokines*. These molecules can exert pro- or anti-inflammatory changes in addition to metabolic alterations. The adipokine leptin can promote proinflammatory cytokine production and activate CD4 and CD8 T cells (Kredel et al., 2014; Lord et al., 1998; Martín-Romero et al., 2000; Procaccini et al., 2013). In contrast, the adipokine adiponectin exerts anti-inflammatory effects by inhibiting tumor necrosis factor-α expression in monocytes and suppressing macrophage and T cell proliferation and IL-10 production (Tilg and Moschen, 2006; Wolf et al., 2004). When mice were induced to develop *Staphylococcus aureus* endocarditis, their serum levels showed significantly decreased adiponectin and significantly increased leptin and visfatin (Schmid et al., 2017).

Obesity is a state of inflammation

Lean adipose tissue is characterized by IL-10 and T helper type 2 cytokine profiles that maintain a homeostatic environment predominated by M2 macrophages, regulatory T cells, eosinophils, and invariant natural killer T cells (Watanabe et al., 2013). In obesity, adipose tissue is infiltrated by large amounts of M1 macrophages, CD8 T cells, T helper type 1 cells, and neutrophils that lead to up-regulation of tumor necrosis factor-α, IL-1, IL-6, and other proinflammatory cytokines (Chung et al., 2018; Cildir et al., 2013; Lumeng et al., 2007). The result is a state of chronic low-grade inflammation that disrupts adipocyte function and leads to metabolic derangements. Tumor necrosis factor-α, produced primarily by adipose tissue-associated M1 macrophages, impairs insulin sensitivity in adipocytes (Cawthorn and Sethi, 2008). IL-17, produced by T cells, and IL-1β, produced by macrophages and potentially by adipocytes themselves, down-regulate adipocyte genes associated with lipolysis and lipogenesis, fatty acid uptake, and adipokine production (Bing, 2015). TBK1, a kinase induced downstream of proinflammatory signaling and NF-κB activation, is significantly more active in adipose tissue of high fat diet-fed mice compared with standard diet-fed mice (Reilly et al., 2013). When activated, TBK1 negatively feeds back on NF-κB and decreases inflammation (Zhao et al., 2018). It exerts a secondary function of repressing cellular respiration and increasing energy storage. TBK1 may be used by adipocytes to decrease the inflammatory milieu of obesity, from which decreased energy expenditure results as a byproduct. When TBK1 is knocked out in murine adipocytes, mice develop exaggerated adipose tissue inflammation, insulin resistance, and weight gain (Zhao et al., 2018). This provides an explanation for the paradoxically decreased energy expenditure in obesity and highlights the potentially causative role that inflammatory cells play in metabolic disease.

Reactive adipogenesis: how the adipogenic response defends against infection

Adipose tissue undergoes local expansion after cutaneous tissue injury, inflammation, and bacterial infection in a phenomenon that we have named *reactive adipogenesis* (Dokoshi et al., 2018; Zhang et al., 2015). This phenomenon has been observed in other species. In dolphins, open wounds are rapidly filled by a thick fatty tissue layer known as blubber within 24 hours of wounding (Zasloff, 2011). Mouse lymph nodes injected with bacterial endotoxin undergo local perinodal adipose hypertrophy, despite an overall decrease in body fat mass, suggesting that adipose tissue can expand when in contact with bacteria (Sadler et al., 2005). Mice housed in germ-free conditions have roughly 30% fewer and 2.8 times smaller dermal white adipocytes compared with mice housed in conventional facilities (Gao et al., 2018). Oral dextran sulfate sodium can be administered to induce acute colitis in mice, which results from increased epithelial wall permeability, impaired mucus secretion, dysregulated defensin production, and increased bacterial burden (Kruis et al., 2013). Recently, Dokoshi et al. (2018) showed that these mice concomitantly developed increased mesenteric fat, submucosal layer thickening, mature adipocyte accumulation, and up-regulation of adipogenic genes, including *Pref1* and *Zfp423*. Histologic examination of tissue from patients with inflammatory bowel disease showed similarly increased *Pref1* expression and staining, suggesting that reactive adipogenesis occurs in both mouse and human colitis (Dokoshi et al., 2018).

Reactive adipogenesis in humans is reflected in fat stranding, in which thickened mesenteric adipose tissue is observed near sites of inflammation on computed tomography imaging as a radiographic sign of diverticulitis, appendicitis, and pancreatitis (Pereira et al., 2004). In Crohn disease, thickened visceral fat (also termed *creeping fat*) proliferates adjacent to diseased gut and provides a visual marker for identifying affected bowel during surgical resection (Paeschke et al., 2017). Adipose tissue hyperplasia in these instances is considered to be a response to increased bacterial translocation through the gut wall (Paeschke et al., 2017). Although adipogenesis in these instances may due to locally recruited immune cells interacting with adipocytes, there is evidence that bacterial antigens can directly trigger adipogenesis. When isolated human omental preadipocytes and adipocytes were infected with *Enterococcus faecalis*, cell proliferation increased by 6-fold in preadipocytes and 2-fold in adipocytes (Zulian et al., 2013).

Reactive adipogenesis defends against infection by producing antimicrobial peptides

The importance of reactive adipogenesis was shown in recent studies, in which researchers discovered that antimicrobial peptides are produced by newly differentiating preadipocytes and that adipose tissue expands in response to pathogens. This essential mammalian immune response may be an evolutionary vestige of more ancient immune defense mechanisms. For example, in *Drosophila* species, an organ known as the fat body consists of adipocytes and encases digestive and reproductive organs (Arrese and Soulages, 2010). In addition to performing roles evolutionarily conserved with mammalian adipocytes, such as metabolic regulation and energy storage, the fat body is the *Drosophila*'s main antimicrobial organ and produces antimicrobial peptides within 90 minutes of encountering bacteria, fungi,

and pathogen-associated molecular patterns (Franz et al., 2018). In rainbow trout (*Oncorhynchus mykiss*), visceral adipose tissue expresses high levels of antimicrobial peptides cathelicidin-2 and hepcidin after infection with live bacterium and bacterial pathogen-associated molecular patterns (Veenstra et al., 2018). In dolphins, the fatty connective tissue known as *blubber* that infiltrates open wounds contains antimicrobial factors, which may account for why dolphins with open soft-tissue wounds resist infection despite continuous exposure to oceanic microbes (Zasloff, 2011). Curiously, blubber is analogous to dWAT in its functional unit (adipocytes) and location (between the skin and muscle layers).

New insight into the biological significance of reactive adipogenesis was gained when 16s rRNA sequencing technologies and histopathologic staining showed that bacteria often enter the reticular dermis and subcutaneous compartments of normal human skin (Nakatsuji et al., 2013). This raised the notion that dermal and subcutaneous fat are not simply sterile spacer areas but are environments in constant flux with commensal and potentially pathogenic microbes. In 2015, Zhang et al. showed that reactive adipogenesis is a direct immune defense response that results in production of the antimicrobial peptide cathelicidin. Intradermal injection of *S. aureus* into mouse back skin caused the dWAT layer to triple in size within 72 hours, which was mediated by proliferation of Pref1- and ZFP423-staining preadipocytes, increased differentiation of preadipocytes into adipocytes, and hypertrophy of existing mature adipocytes (Zhang et al., 2015). When adipogenesis was inhibited in vivo and dWAT did not expand, mice developed greater lesion sizes and bacteria within their bloodstreams despite normal neutrophil infiltration (Zhang et al., 2015). These observations support a model by which the process of cathelicidin production during reactive adipogenesis provides a previously unrecognized but essential immune defense function (Figure 2b and c). This response has since been validated in other models (Schmid et al., 2017) and extended to show that it is also important to defend against bacterial penetration of the colon after injury (Dokoshi et al., 2018).

The mechanism by which adipocytes recognize and respond to bacteria may involve TLR2. Treatment of both undifferentiated and mature 3T3-L1 adipocytes with TLR2 ligands Pam3Cys and MALP-2 led to significantly increased expression of cathelicidin, IL-6, IL-8, and MCP-1 (Schmid et al., 2017). Additionally, both TLR2 and cathelicidin gene expression increase significantly during early adipogenesis, with TLR2 briefly preceding cathelicidin up-regulation (Schmid et al., 2017). Other mechanisms for recognition and response to infection are likely to be uncovered with research in the future.

OTHER NONMETABOLIC FUNCTIONS OF dWAT

Hair cycling

The dWAT surrounding the hair follicle expands during anagen and regresses during telogen in an apparent complex interplay between hair follicles and adipocytes (Chase et al., 1953; Foster et al., 2018; Kruglikov and Scherer, 2016a). Hair follicles in anagen can trigger dWAT hyperplasia and hypertrophy via Wnt signaling production (Kruglikov and Scherer, 2016a), leading to 20%–40% new adipocytes by mid-anagen (Schmidt and Horsley, 2012). In late anagen, mature adipocytes produce maximal levels of BMP2, which can maintain hair follicles in a quiescent state, preventing further anagen (Plikus et al., 2008; Schmidt and Horsley, 2012). In early telogen, mature adipocytes produce maximal levels of BMP2, which helps maintain hair follicles in a quiescent state, preventing new antigen initiation (Plikus et al., 2008; Schmidt and Horsley, 2012). Reciprocal signaling from adipose precursors to hair follicles is also necessary for hair cycling, because mouse models devoid of immature adipose precursors show a defect in progression from telogen to anagen, and this is rescued by preadipocyte transplantation (Festa et al., 2011; Schmidt and Horsley, 2012).

Thermogenesis

The dWAT layer thickens during decreased ambient temperature. Kasza et al. (2014) reported that BALB/c mice housed at room temperature (21–24 °C) developed thicker dWAT layers, which thinned out by 80% when the mice were transferred to warmer housing conditions (29–31 °C) for 2 weeks (Kasza et al., 2014). The authors noted that dermal and subcutaneous adipose tissue are separate layers in mice and did not report tissue expansion in the subcutaneous adipose layer. A fully expanded dWAT layer can reduce heat loss by 2-fold in mice housed in ambient temperatures (Alexander et al., 2015). Mice that lack dWAT but have otherwise preserved white and brown adipose tissue show chronic activation of thermal defenses, suggesting that dermal adipocytes have an important function in preserving thermal homeostasis (Alexander et al., 2015). Although several adipose depots respond to cold stress, dWAT expands with ambient temperature changes but not at 4 °C, suggesting that dermal adipocytes respond to different temperature cues. Traditional thermogenic responders include brown adipose tissue, which is activated rapidly during 4 °C challenge, and subcutaneous white adipose tissue, which can undergo beige-ing or browning after chronic exposure to temperatures of 4–8 °C (Ikeda et al., 2018). Beige (or brite) adipocytes are multilocular adipocytes capable of expressing high levels of uncoupling proteins for thermogenesis and are derived directly from white adipocytes or differentiate de novo in white adipose depots (Ikeda et al., 2018; Rosenwald et al., 2013; Wu et al., 2012). One may speculate that the outermost dWAT has evolved to maintain thermal homeostasis on a day-to-day basis, during which organisms typically encounter ambient temperature fluctuations, but that internal adipose sites have evolved as emergency reserves for protection during rare scenarios of freezing.

Wound healing

Dermal adipocytes repopulate skin wounds after inflammation and direct fibroblast recruitment. In full-thickness cutaneous wounds in murine skin, small perilipin$^+$ adipocytes appear in the wound bed on days 5–7 during the proliferative phase of wound healing, directing fibroblast migration into the wound (Schmidt and Horsley, 2013). Inhibition of adipogenesis by pharmacological inhibitors or genetically mutated mouse models impairs fibroblast migration to the wound center despite preservation of keratinocyte

re-epithelialization, macrophage recruitment, and fibroblast proliferation at the wound edge (Schmidt and Horsley, 2013). This results in failure of epithelial integrity after 2 weeks and spontaneous reopening of the wound. Multiple fibroblast populations participate in this process and interact with macrophages during wounding (Shook et al., 2018).

Fibrosis and scarring

Dermal adipocytes have been implicated in the pathogenesis of systemic sclerosis (Marangoni et al., 2015). Systemic sclerosis is associated with a loss of dermal adipocytes and accumulation of myofibroblasts, which exert contractile behavior, deposit collagen, and produce profibrotic cytokines. Myofibroblasts are responsible for pathologic fibrosis in many tissue types, including the bone marrow, heart, liver, lungs, kidney, and skin (Hinz et al., 2007). In the skin, myofibroblasts are classically viewed as differentiating directly from local dermal fibroblasts during inflammation and wound healing (Desmoulière et al., 2005). However, myofibroblasts in wounds have also been traced to pericytes, peripheral blood fibrocytes, and smooth muscle cells, forming by way of epithelial-to-myofibroblast and endothelial-to-myofibroblast transitions (Abe et al., 2001; Rajkumar et al., 2005). Using lineage tracing and ex vivo differentiation assays in mouse skin, Marangoni et al. (2015) showed that dermal adipocytes may serve as a source of myofibroblasts by directly trans-differentiating into these Sma^{+} cells when exposed to profibrotic agents such as transforming growth factor-β or bleomycin, suggesting that an adipocyte-to-myofibroblast transition is also possible (Figure 2a). Some have postulated that the adipocyte-to-myofibroblast transition could be involved in skin aging (marked by loss of facial dWAT volume and replacement with fibrotic adipocytes) (Wollina et al., 2017) and androgenic alopecia (Kruglikov and Scherer, 2017). An important role for transforming growth factor-β in driving the conversion of dermal fibroblasts from cells with adipogenic to fibrotic potential has been shown during aging in mice and humans (Zhang et al., 2019).

The adipocyte-to-myofibroblast transition appears to be a reversible, fluid process in which myofibroblasts serve as a source of new adipocytes in wounds. Plikus et al. (2017) observed that large cutaneous wounds were associated with new dermal adipocyte formation, but only in areas surrounding hair follicles, which could produce bone morphogenetic protein (i.e., BMP) and reprogram surrounding myofibroblasts into adipocytes (Plikus et al., 2017). Myofibroblasts derived from human keloids developed into adipocytes when treated with BMP or co-cultured with human hair follicles in vitro (Plikus et al., 2017). These findings suggest a new source of adipogenic progenitor cells and that myofibroblasts may be reprogrammed into adipocytes to prevent or improve scarring.

CONCLUSIONS

In this review, we sought to introduce several independent lines of experimental evidence that, when considered together and in the context of the skin, make a compelling argument that dermal fibroblast cells in the adipocyte lineage play an essential role in immune defense. Dermal white adipose tissue has been an underappreciated, but clearly important, immune layer in the skin. It is tempting to speculate that the participation of adipocytes in local and systemic immune responses, and the reactions of DWAT to skin injury and inflammation, may provide an explanation between cardiovascular comorbidities and inflammatory skin diseases such as psoriasis (Kruglikov and Wollina, 2017). Other dermatologic disorders, such as panniculitis erythema nodosum, take on new significance when the active participation of adipocytes as immunocytes is considered in the context of their unknown pathophysiology. Much future investigation into this important layer of immune defense is warranted.

CONFLICT OF INTEREST

RLG is a co-founder, scientific advisor, consultant and has equity in MatriSys Biosciences and is a consultant, receives income and has equity in Sente.

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