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The Role of Adipocytes in Tissue Regeneration and Stem Cell Niches

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Abstract

Classically, white adipose tissue (WAT) was considered an inert component of connective tissue but is now appreciated as a major regulator of metabolic physiology and endocrine homeostasis. Recent work defining how WAT develops and expands in vivo emphasizes the importance of specific locations of WAT or depots in metabolic regulation. Interestingly, mature white adipocytes are integrated into several tissues. A new perspective regarding the in vivo regulation and function of WAT in these tissues has highlighted an essential role of adipocytes in tissue homeostasis and regeneration. Finally, there has been significant progress in understanding how mature adipocytes regulate the pathology of several diseases. In this review, we discuss these novel roles of WAT in the homeostasis and regeneration of epithelial, muscle, and immune tissues and how they contribute to the pathology of several disorders.

Keywords

adipose tissue; regeneration; skin; adipocyte

INTRODUCTION

In vertebrates, mature white adipocytes store energy in the form of triglycerides, control organismal energy balance and metabolism through hormone or adipokine secretion, and provide mechanical cushioning for organs (Rosen & Spiegelman 2006). Pathologically, the expansion of white adipose tissue (WAT) during obesity is associated with metabolic and cardiovascular disease, with defects in wound healing, and with cancer. Recent studies have highlighted novel roles of WAT in tissue regeneration and stem cell regulation, highlighting the central role of adipose tissue in multiple aspects of organismal biology. In this review,

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we focus on the roles of adipocytes in skin, mammary gland (MG), and skeletal muscle homeostasis and repair.

TYPES OF ADIPOSE TISSUE

Mammals have two major types of adipose tissue with distinct functions: brown adipose tissue (BAT) and WAT. Mature adipocytes in BAT contain multiple small lipid droplets and a high number of mitochondria, whereas mature adipocytes in WAT contain few mitochondria and a unilocular lipid droplet for triglyceride storage (Berry & Rodeheffer 2013). BAT generates heat from a lipolytic process that involves uncoupling of the mitochondrial proton gradient from ATP generation (Nicholls & Locke 1984). In contrast, the triglycerides in WAT are released and transported to tissue for use as energy through oxidation (Frayn et al. 2006).

Both BAT and WAT develop in discrete locations within the body as large collections of adipocytes that are identified as specific depots. Large depots of WAT found in the subcutaneous and visceral regions of mammalian organisms have been studied due to the association of visceral fat with metabolic disease (Lee et al. 2013). The subcutaneous WAT (sWAT) and visceral WAT (vWAT) depots display distinct adipokine secretions and rates of lipolysis and triglyceride synthesis (Tchkonia et al. 2013). Whereas several recent reviews have discussed the biology, function, and regulation of traditional WAT depots (Rosen & Spiegelman 2006), here we focus on the role of WAT in additional depots associated with the skin, MG, bone marrow, and skeletal muscle.

BIRTH AND DYNAMICS OF DISTINCT ADIPOSE DEPOTS

The development and maintenance of WAT occur through distinct mesenchymal precursor cells that differentiate into mature adipocytes. Genetic lineage-tracing tools in mice have revealed that the various depots develop at distinct times and from specific mesenchymally derived progenitor populations (reviewed in Sanchez-Gurmaches & Guertin 2014). For instance, dorsal-anterior adipocyte depots arise from *Myf5*- or *Pax3*-expressing precursor cells, and cephalic adipocytes arise from *Sox10*-expressing neural crest precursors (Billon et al. 2007). In the skin, *delta-like homologue 1* (*Dlk1*)-expressing embryonic mesenchymal precursors generate both dermal fibroblasts and adipocytes until E16.5, when they become restricted in their contribution to the dermal WAT (dWAT) (Driskell et al. 2013, 2014; Wojciechowicz et al. 2008, 2013), and lipid-filled mature adipocytes are present in the dermis of mice following the formation of hair follicles (Hausman et al. 1981) (Figure 1). In mice, the three anterior MG pairs form in thoracic WAT depots, which are partially associated with BAT, whereas two posterior MG pairs develop in the inguinal WAT pad (Gouon-Evans & Pollard 2002, Hovey et al. 1999).

Studies of human adipocytes labeled with stable isotopes during nuclear weapons testing revealed that turnover of mature adipocytes is approximately 10% per year (Spalding et al. 2008). However, WAT depots can expand or reduce their mass dramatically in response to nutritional states (Krotkiewski & Björntorp 1975, Krotkiewski et al. 1983). The expansion of WAT can occur through hypertrophy (an increase in mature adipocyte size) or hyperplasia

(an increase in mature adipocyte number). During states of overnutrition, the accumulation of lipid rapidly promotes hypertrophy of mature adipocytes (Krotkiewski et al. 1983). A major advance in our understanding of the regulation of WAT hyperplasia came with in vivo identification of adipocyte precursor cells (APs) within WAT that are identified by several cell surface proteins, including Sca1 and CD24, and that express Pdgfrα (Berry & Rodeheffer 2013, Joe et al. 2010, Rodeheffer et al. 2008).

In response to overfeeding, individual WAT depots display distinct mechanisms of growth. In humans, upper-body sWAT depots display hypertrophic growth, whereas hyperplasia contributes to expansion of depots below the waist (Tchoukalova et al. 2010). Distinct responses of individual depots to dietary cues also occur in mice. Male mice fed a high-fat diet (HFD) display hyperplasia in the visceral depot, but not in the sWAT (Jeffery et al. 2015). These hyperplastic responses are in part due to proliferation and differentiation of APs in response to HFD in an Akt-dependent manner (Jeffery et al. 2015).

Dramatic changes in WAT mass can also occur in dWAT in response to multiple stimuli. As hair follicles regress and grow cyclically during the hair cycle, adipocytes regress and expand in parallel with the hair follicle to double the size of the dermis (Chase et al. 1953). During hair follicle growth, dWAT displays a dynamic and rapid expansion of mass due to both hypertrophy and hyperplasia via $Sca1^{+}$ AP proliferation (Festa et al. 2011). Recent work has also revealed that dWAT expands in mice in response to skin bacterial infection (Zhang et al. 2015). Interestingly, whereas cold stress can induce alterations in white adipocytes toward a brown adipose phenotype in other depots (Jankovic et al. 2015), dWAT expands in response to cold stress (Kasza et al. 2014).

Adipose tissue is also highly dynamic during the pregnancy, lactation, and involution cycle in the MG (Figure 1). MG adipocytes expand by almost 20% during pregnancy (Elias et al. 1973, Pujol et al. 2006). During lactation, the MG epithelium of rodents differentiates to produce milk, and stromal adipocytes are depleted (Elias et al. 1973). Cessation of lactation results in a robust regression of MG epithelium (Watson 2006), and the stromal adipose tissue in mice expands rapidly to repopulate the stroma within a few days (Elias et al. 1973). These dynamic changes in MG WAT have been reported to occur through transdifferentiation from epithelial cells in the gland (Morroni et al. 2004). Future studies exploring whether resident APs or other cell types contribute to WAT dynamics in the MG will be interesting avenues of investigation.

In addition to developing in depots within the skin and MG, WAT develops in skeletal muscle during muscle atrophy (Figure 1). Tissue-resident APs exist in skeletal muscle and, as in other depots, express Pdgfrα, Sca1, and CD34 (Joe et al. 2010, Uezumi et al. 2010), similar to APs found in WAT depots (Festa et al. 2011, Rodeheffer et al. 2008). These cells have the dual capacity to generate fibroblasts and adipocytes and are thus thought to represent a fibro-adipogenic progenitor (FAP). Not surprisingly, other muscle locations, such as cardiac muscle, also show the presence of adipocytes that are generated by stromal cells (Sommariva et al. 2016). Although skeletal muscle adipose tissue emerges in different injury and disease states, whether WAT expands in skeletal muscle in other conditions in rodents is unclear.

An additional depot of WAT exists in the marrow space of bone. Although bone marrow WAT (mWAT) stores triglycerides, as does WAT in other depots (Tavassoli et al. 1977) (Figure 1), the size of mature adipocytes in mWAT is smaller. Surprisingly, in contrast to the reduction of most WAT depots with caloric restriction, mWAT expands in the anorexic mouse and human (Bredella et al. 2009, Devlin et al. 2010, Fazeli et al. 2012). $Sca1^+$, $CD24^+$ adipogenic precursors present in other WAT depots are not found in mWAT (Fazeli et al. 2013). Yet, mature adipocytes within mWAT do form from precursor cells that express *Pdgfra*, *Osterix1*, *Leptin receptor*, and *Nestin* (Mizoguchi et al. 2014, Morikawa et al. 2009, Pinho et al. 2013, Zhou et al. 2014), suggesting that the cellular progenitors that maintain mWAT may be distinct from those of other WATs. Thus, there may be a mesenchymal multipotent precursor cell in bone marrow capable of giving rise to multiple lineages, including bone, cartilage, and mWAT.

FUNCTIONS OF ADIPOSE DEPOTS IN TISSUE DEVELOPMENT, HOMEOSTASIS, AND REGENERATION

Skin

Mature adipocytes are one of the most abundant cell types within the skin's dermis, which supports the epithelial keratinocytes of the epidermis. Although dWAT was previously believed to merely provide insulation and protective cushioning, tremendous strides have been made in our understanding of how dWAT contributes to skin biology, supporting the current view that dWAT is central to cutaneous function.

Hair follicle regeneration—One role of dWAT is the intimate regulation of hair follicle growth by adipocyte lineage cells (Figure 2). The growth of hair follicles in skin is tightly regulated and can be divided into specific stages (Schneider et al. 2009, Stenn & Paus 2001). The activation of hair follicle growth (anagen) involves the proliferation of epithelial stem cells located in the bulge region of the hair follicle (Blanpain et al. 2004, Cotsarelis et al. 1990, Zhang et al. 2009) and their communication with the mesenchymal component of the hair follicle, the dermal papillae (Jahoda et al. 1984, Rompolas et al. 2012). Following anagen, the hair follicle enters into a regression state (catagen) followed by a phase of relative quiescence termed telogen.

Mature adipocytes in dWAT may be key regulators of the rest stage of the hair cycle through the expression of *Bmp2* mRNA (Festa et al. 2011, Plikus et al. 2008) (Figure 2). BMP signaling in hair follicle stem cells is required for their quiescence (Kandyba et al. 2013, Kobielak et al. 2007), and the increased formation of mature adipocytes during hair growth leads to enhanced levels of Bmp ligand expression in the dermis (Plikus et al. 2008). The combination of BMP expression by adipocytes and that by dermal papillae cells (Sennett & Rendl 2012) may suppress stem cell activity. Later in hair growth, adipocyte-derived BMPs may also support hair lineage specification and/or differentiation (Kobielak et al. 2003, Kwan et al. 2004) because hair follicle lineage cells detect BMP ligands at specific stages of differentiation (Genander et al. 2014).

In addition, immature APs can stimulate hair follicle stem cell activity (Festa et al. 2011). Genetic and pharmacological loss of APs in the skin delays hair growth initiation. Furthermore, intradermal transplantation of APs activates hair follicle growth, indicating that APs are a key component of the hair follicle stem cell niche. Mature intradermal adipocytes express the adipokine leptin and may also stimulate hair growth, as treatment of human hair follicle organ cultures with leptin can enhance hair shaft length (Yang et al. 2015), and injection of leptin into mouse skin can induce activation of hair follicle stem cells and hair growth (Sumikawa et al. 2014, Watabe et al. 2014). Whether adipocytes signal directly to epithelial cells or act through the dermal papilla remains to be determined.

The interaction between dWAT and hair follicles seems to be bidirectional, as activation of hair follicle growth through epidermal activation of Wnt/β-catenin stimulates expansion of dWAT (Donati et al. 2014) (Figure 2). Although the precise mechanism is not known, in vitro experiments suggest that keratinocytes secrete proadipogenic molecules such as Bmp2, Bmp6, and Igf2 (Donati et al. 2014). Unanswered questions remain regarding the interaction between the hair follicle and intradermal adipocytes. Are signaling pathways activated during skin adipogenesis, as are pathways activated during adipogenesis in other depots? Do alterations in dWAT contribute to pathologies with defective hair follicle growth? Addressing these questions will provide a better understanding of the relationship between adipose tissue, epidermis, and hair growth and could lead to new treatments to remedy hair loss.

Wound healing—Although changes in dWAT were observed in association with wound healing decades ago (Montagna et al. 1988), understanding of how adipocyte lineage cells aid skin repair following injury is in its infancy. Although various cells with mesenchymal stem cell markers are important in dermal wound healing, adipose-derived stem cells are an attractive substitute for mesenchymal stem cells from bone marrow because the former cells are more easily accessible, are more available, and are often discarded as medical waste (Condé-Green et al. 2016). Multiple groups have investigated the role of adipocyte lineage cells during skin repair in an attempt to harness their therapeutic potential.

Intradermal injection of adipose-derived stem cells following injury accelerates dermal wound healing in mice (Kim et al. 2007). These cells survive for up to one year after dermal injection, without detection in distant immune organs or tumor formation at the site of injection (Koellensperger et al. 2014). A common observation across these models is an increase in angiogenesis; this increase is mediated by vascular endothelial growth factor (VEGF). Consequently, using adipose-derived stromal cells as delivery agents for VEGF to dorsal wounds accelerated healing (Nauta et al. 2012, Song et al. 2012). Even though adipose-derived stem cells can accelerate wound healing, the heterogeneity of cells described as adipose-derived (mesenchymal) stem or stromal cells do not have a universal definition or preparation protocol (Baer & Geiger 2012). Adherent cells isolated from the stromal vascular fraction of enzymatically digested adipose tissue are frequently used for transplantation. This adherent fraction consists of APs, fibroblasts, and various immune cells. Additionally, confusion persists over the boundaries, relationships, and classification of closely associated WAT depots in humans, as the terms dermal, intradermal,

subcutaneous, hypodermis, or simply skin are inaccurately used interchangeably (Driskell et al. 2014).

In addition to immature adipocyte lineage cells, mature adipocytes have been implicated in regulating skin wound healing. Multiple adipokines can alter the rate of wound repair. The two primary adipokines that have been investigated during wound healing are adiponectin and leptin. The most striking wound healing phenotype in adiponectin-deficient mice is severely delayed reepithelialization. Cultured keratinocytes treated with adiponectin show increased proliferation and migration through ERK signaling and in vivo administration of adiponectin to mouse skin wounds, accelerated wound healing, and reepithelialization (Jin et al. 2015, Salathia et al. 2012, Shibata et al. 2012). Administration of adiponectin in an ear punch model accelerated reepithelialization and wound closure so effectively that wound contraction and complete dermal repair were delayed (Salathia et al. 2012). Interestingly, another group demonstrated that adiponectin can enhance apoptosis, suggesting that decreased levels of adiponectin in diabetic ulcers may contribute to peripheral hyperkeratosis through persistence of the wound-associated hyperthickened epithelium (Kawai et al. 2008). These data demonstrate that adiponectin is an important factor for driving reepithelialization of skin wounds and a promising therapeutic target for delayed wound healing.

In addition to adiponectin, leptin promotes wound healing. Leptin signaling can enhance reepithelialization and angiogenesis following injury (Frank et al. 2000, Ring et al. 2000, Sierra-Honigmann et al. 1998). The systemic or local application of leptin to leptin-deficient (*ob/ob*) mice accelerates reepithelialization and contraction of full-thickness skin wounds independently of revascularization (Frank et al. 2000, Ring et al. 2000).

Although the majority of wound healing studies have focused on revascularization and reepithelialization of wound beds, deep dermal fat is present within hypertrophic scars (Matsumura et al. 2001), suggesting a relationship between dWAT and extracellular matrix (ECM) deposition. Interestingly, stromal cells from skin-associated adipose tissue have increased levels of collagen 1, alpha smooth muscle actin (αSMA), and lysyl hydroxylase-2b (a critical enzyme in collagen cross-linking) compared with levels in total dermis (van den Bogaerdt et al. 2009). Additionally, purified human adipose-derived stem cells can increase human dermal fibroblast proliferation, migration, and production of collagen 1 (Kim et al. 2007). These data suggest that the local WAT environment may be promoting a more fibrotic phenotype of resident fibroblasts. We have shown that adipocytes are required for fibroblast repopulation of dorsal skin wound beds by triggering fibroblast migration (Schmidt & Horsley 2013). A-ZIP mice, which lack mature adipocytes, initially have normal reepithelialization of wound beds but subsequently show impaired fibroblast repopulation of wound beds. An altered fibroblast response was not seen in diabetic *ob/ob* mice, suggesting that this result is not the sequela of systemic metabolic derangement but is rather due to the lack of adipocytes. This study was confirmed using pharmacological antagonists of PPARγ, which inhibits adipogenesis and results in reduced wound bed fibroblast repopulation (Schmidt & Horsley 2013). Impaired fibroblast reconstitution and ECM deposition resulted in recurring wounds in these models.

These findings demonstrate the tremendous translational value of adipocyte lineage cells in cutaneous wound healing. In the future, it is important for the field to have more unified definitions of adipose-derived cells and for future work to parse out the differences in function between adipose-derived stem cells, adipocytes, and other cells present in adipose tissue during wound healing beyond angiogenesis and fibroblast deployment.

Thermoregulation—The role of the skin in thermoregulation is not fully understood (Romanovsky 2014). Recent evidence suggests that dWAT responds to and may regulate thermoregulation in response to cold stress (Kasza et al. 2014). Kasza et al. (2014) showed that cold stress in mice can expand dWAT thickness in addition to its additional physiological changes in activating uncoupling protein-1 (UCP-1) in BAT and a cold stress response in liver glycogen and oxygen consumption. Interestingly, in mice lacking the heparin sulfate proteoglycan syndecan-1 ($Sdc^{-/-}$ mice), dWAT thickness was significantly decreased, whereas other WAT depots were not dramatically altered. In response to overnight fasting at room temperature, $Sdc^{-/-}$ mice exhibited lethargy, systemic metabolic defects, and activation of UCP-1 and stress-induced p38α in BAT, similar to what is observed in response to cold stress. This phenotype was prevented by housing mice at thermoneutral conditions (31°C), indicating that loss of syndecan-1 leads to systemic cold stress in mice housed at 21°C. The authors demonstrated that loss of syndecan-1 resulted in decreased adipogenesis in culture and that administration of the PPARγ agonist rosiglitazone was able to rescue dWAT thickness and prevent the cold stress–induced response of $Sdc^{-/-}$ mice housed at 21°C (Kasza et al. 2014). Interestingly, the diminished dWAT thickness in $Sdc^{-/-}$ mice was rectified during hair growth, indicating that adipogenic and hypertrophic signals during hair cycling do not rely on syndecan-1. How thermal changes control dWAT and the role of dWAT in thermal protection will be interesting areas of future investigation.

Mammary Gland

Although WAT composes approximately 80% of the MG stroma, its function has only recently been explored. Several factors secreted by adipocytes can promote MG tumorigenesis (Iyengar et al. 2003, 2005) and differentiation of mammary epithelial organoids (Howlett & Bissell 1993, Zangani et al. 1999). The development of a functional mammary ductal tree structure requires mature adipocytes because lipodystrophic A-ZIP mice (Moitra et al. 1998) and a mouse model with inducible loss of adipocytes (Pajvani et al. 2005) display rudimentary mammary anlagen and severely distended mammary ducts (Couldrey et al. 2002, Landskroner-Eiger et al. 2010). Furthermore, the transplantation of embryonic mammary epithelium, single MG stem cells, or sweat gland epithelial progenitors into WAT is sufficient to induce morphogenesis of the mammary ductal tree (Lu et al. 2012, Sakakura et al. 1982, Stingl et al. 2006). Interestingly, leptin may be involved in mammary gland development because *ob/ob* mice and *db/db* mice (mice lacking the leptin receptor) lack postnatal ductal epithelium (Hu et al. 2002).

Skeletal Muscle

Although adipose tissue in other depots can positively affect tissue function, the presence of skeletal muscle–associated adipose tissue is associated mostly with muscular disorders

(Wallace & McNally 2009) and is correlated with insulin resistance and increased body mass index (Albu et al. 2005, Yim et al. 2007). Whereas defective wound repair occurs in skeletal muscle of *ob/ob* and *db/db* mutant mice (Nguyen et al. 2011), mature adipocytes are sparse in young, healthy skeletal muscle, and an abundant pool of FAPs resides in skeletal muscle (Joe et al. 2010; Uezumi et al. 2010, 2011). Whereas mature adipocytes may impair muscle physiology, FAPs contribute to successful wound healing. Three to four days after acute muscle injury, FAPs are more abundant at wound edges and dramatically increase proliferation (Joe et al. 2010, Uezumi et al. 2010). Coculturing myogenic precursors with FAPs enhances muscle differentiation, possibly through expression of antiadipogenic, promyogenic Igf-1, IL-6, Wnt1, Wnt3A, and Wnt5A (Joe et al. 2010). Interestingly, a similar population of cells exists in human skeletal muscle (Arrighi et al. 2015, Uezumi et al. 2014). Given that degenerative muscle fibers are able to induce adipogenesis (Hosoyama et al. 2009), accumulation of mature adipocytes may be secondary to, and not the cause of, deterioration of muscle tissue. It will be exciting for future studies to determine whether mature adipocytes have a functional contribution to the dysfunction of muscle tissue seen in disease states.

Immunity

Communication between adipocytes and immune cells is an emerging area with tremendous implications for tissue regeneration and stem cell biology. Mesenchymal precursors within the bone marrow that can form adipocytes are important for organizing hematopoiesis by regulating hematopoietic stem cells through BMP (Zhang et al. 2003) and Tie2 (Arai et al. 2004) signaling. Adipocytes within mWAT may also regulate hematopoiesis (Naveiras et al. 2009). Outside of mWAT, several mouse models of obesity display an increase in diverse immune cell subsets in vWAT (Kanneganti & Dixit 2012). Indeed, salicylate anti-inflammatory agents were shown in the early 1900s to ameliorate diabetic symptoms in humans. However, only recently has the importance of WAT depots outside of the bone marrow in regulating immunity come to light.

In a lean state, adipose tissue macrophages (ATMs) are skewed toward an anti-inflammatory phenotype (described as M2, or alternatively activated) (DiSpirito & Mathis 2015, Kanneganti & Dixit 2012). This skewing of ATMs is necessary to support tissue expansion, and WAT signaling to the immune system is required to activate adipogenesis in vWAT during short-term HFD (Asterholm et al. 2014). As adipose tissue expands, ATMs stimulate angiogenesis through increased production of PDGFβ (Pang et al. 2008). Although the initial inflammatory process is beneficial for tissue growth, prolonged adipose tissue inflammation can lead to fibrosis, hindering adipocyte expansion and preventing further lipid storage (Khan et al. 2009, Pasarica et al. 2009). Continued expansion of WAT during obesity results in excess lipids and increased levels of macrophage chemoattractant-1 (MCP-1), which rapidly induces infiltration of a large number of ATMs into vWAT (Schipper et al. 2012, Xu et al. 2003) that can induce insulin resistance (reviewed in Osborn & Olefsky 2012). These ATMs are similar to inflammatory macrophages described in other tissues (DiSpirito & Mathis 2015, Lumeng et al. 2007, Nguyen et al. 2007). Ablation of inflammatory macrophages (Patsouris et al. 2008, Weisberg et al. 2006) or deletion of IKK-β (Arkan et al. 2005), JNK1 (Solinas et al. 2007), the insulin receptor (Mauer et al. 2010),

or fatty acid–binding protein 4 (FABP4) (Furuhashi et al. 2008) in macrophages protects mice from obesity-induced insulin resistance.

Other local immune cells, such as regulatory T cells (T_{regs}), influence macrophage phenotype. T_{reg} secretions elicit a Th2 immune response that promotes anti-inflammatory ATM gene expression and suppresses inflammatory immune responses that promote inflammatory macrophage migration in WAT during obesity (Feuerer et al. 2009) and aging (Cipolletta et al. 2015, Kolodin et al. 2015, Vasanthakumar et al. 2015). Increasing the number of T_{reg} cells can improve insulin sensitivity during obesity (Feuerer et al. 2009). Furthermore, deletion of *PPARG* in T_{regs} resulted in reduced age-related weight gain and improved metabolic parameters, including insulin resistance, glucose tolerance, and calorie expenditure (Bapat et al. 2015).

Given the importance of inflammatory cytokines and macrophage phenotype in regenerative processes in many tissues after injury (Goren et al. 2010, Lucas et al. 2010, Sciorati et al. 2016), the impact of adipocytes on macrophage phenotype may influence tissue regeneration more broadly. Not only do skin macrophages influence hair follicle activation (Castellana et al. 2014), but unique macrophage phenotypes are associated with various phases of skin regeneration after injury (Daley et al. 2010, Mirza & Koh 2014). Macrophages are also required for the involution of the MG epithelium that is associated with MG WAT expansion (O'Brien et al. 2010). Given that obesity induces inflammatory pathways beyond vWAT, such as in the liver (Cai et al. 2005) and muscle (Bandyopadhyay et al. 2005, Itani et al. 2002), the strong correlation between obesity, inflammation, and comorbidity with many diseases underscores the importance of uncovering the complex interactions between immune cells and adipocytes. It is promising that future studies could uncover adipocyte and immune cell interactions that regulate reparative processes and disease states in different tissues.

ADIPOCYTES IN CUTANEOUS DISEASE

Just as adipose tissue contributes to proper function in various tissues, dysfunction of adipose tissue contributes to impaired physiology in multiple tissues. Several dermatological conditions in humans are associated with altered dermal adiposity. Recent studies have demonstrated a central role of adipocytes in multiple disease states. Below, we discuss how dWAT in a lean state has a protective role in skin homeostasis, how loss of adipocytes corresponds with the progression of certain cutaneous diseases, and how altered adipocyte biology associated with obesity promotes disease progression.

Skin Disorders

Various lipodystrophic conditions are characterized by hair loss or alopecia concomitantly with a loss of adipose tissue; however, a causative role of human dWAT in hair follicle maintenance has not been described (Fukumoto et al. 2009, Hegele 2005, Jeninga et al. 2009). Additionally, as many as 61% of patients suffering from anorexia have hair loss or fragile hair (Strumia 2009), along with lower levels of leptin (Janas-Kozik et al. 2011, Uzum et al. 2009). Hyperkeratosis, immune cell infiltration, and alopecia can also be observed in the scalps of patients experiencing lipoedema (Bridges et al. 2000, Fukumoto et al. 2009,

Piraccini et al. 2006), and these symptoms can worsen as adiposity increases. Moreover, lipodystrophic individuals with mutations in *PPARG* frequently exhibit hyperpigmentation, hirsutism, and cutaneous eruptive xanthomata (Hegele 2005, Herrmann et al. 2003). Future studies are required to determine whether changes in skin biology are a direct result of altered dWAT or whether changes in adiposity are a symptom of the disease.

Infection

A recent study demonstrated that dermal adipocytes contribute directly to the innate immune response following skin infection (Zhang et al. 2015). Shortly after *Staphylococcus aureus* infection of mouse back skin, local AP proliferation and hypertrophy of mature adipocytes lead to a dramatic expansion of dWAT (Figure 3). As adipose tissue expands, mature adipocytes produce the antimicrobial peptide cathelicidin. Pharmacological inhibition of adipogenesis during infection reduced host ability to combat infection and resulted in greater numbers of *S. aureus* colony-forming units. Additionally, cultured human adipocytes increased expression of cathelicidin in response to *S. aureus*, indicating that human adipocytes may also contribute to innate immunity following infection (Zhang et al. 2015). Interestingly, common inflammatory skin diseases such as atopic dermatitis, psoriasis, and rosacea are characterized by defects in cutaneous cathelicidin. Future studies will be required to determine whether changes in adipocyte-derived cathelicidin contribute to the pathology of these diseases.

Fibrosis

Just as adipocytes and their precursor cells play important roles in scar deposition during wound healing, it is becoming increasingly appreciated that adipocytes may play key roles in the development of fibrosis. Fibrosis is a chronic pathology characterized by excessive and chronic ECM deposition in the interstitial spaces of affected organs, ultimately leading to increased organ stiffness and loss of function (Friedman et al. 2013, Wynn 2008). In dermal fibrosis, deposition of fibrous ECM often occurs in conjunction with subcutaneous adipose tissue atrophy (Figure 3), a phenomenon observed in both human scleroderma patients and animal models (Fleischmajer et al. 1971, Smith & Chan 2010). Fibrosis also manifests in many diverse pathologies, including obesity, epithelial tumors, and cancer cachexia (Bing et al. 2006, Bochet et al. 2013, Sun et al. 2013).

The primary producer of ECM in fibrosis is an activated cell type known as the myofibroblast, a contractile, fibroblast-like cell that produces large amounts of collagens and SMA (Gabbiani et al. 1971, Hinz et al. 2012). The origins of these cells are largely debated due to the diversity of lineage-tracing schemes in different fibrosis models, as we recently reviewed (Ebmeier & Horsley 2015). Recent evidence has pointed to a possible adipocyte origin of some myofibroblasts in dermal fibrosis. Through the use of a lineage-tracing strategy in which adiponectin-driven Cre recombinase was used to label mature adipocytes with tdTomato, adiponectin-traced cells lost labeling with the adipocyte lipid vesicle marker perilipin and colocalized with αSMA in bleomycin-induced dermal fibrosis (Marangoni et al. 2014). This development was accompanied by a morphological change of the cells from a round adipocyte-like morphology to a spindle-shaped fibroblast-like morphology. The authors also reported that a loss of adipogenic gene expression preceded increased

expression of fibrogenic genes and reported increased dermal thickness associated with dermal fibrosis. In a subsequent study, Martins et al. (2015) observed that a profibrotic protein termed FIZZ1 induced cultured adipocytes to acquire myofibroblast characteristics, including lipolysis and increased expression of αSMA and collagen 1. FIZZ1 was upregulated in mice with bleomycin-induced fibrosis, and deletion of FIZZ1 from the genome reduced the severity of bleomycin-induced fibrosis (Martins et al. 2015).

Not only are mature adipocytes implicated in the development of fibrosis, but APs also have a functional relationship with fibroblasts. In multiple models of fibrosis and acute injury, cells that share characteristics with APs become activated and lead to myofibroblast accumulation (reviewed in Ebmeier & Horsley 2015). APs in culture can be stimulated to acquire an activated fibroblast phenotype with decreased adipogenic potential when stimulated with cytokines or fibrotic factors such as TGFβ1 or bleomycin (Ohgo et al. 2013). APs also require the ability to remodel collagen to differentiate, suggesting that increased ECM produced during fibrosis may mechanically constrain adipogenesis (Chavey et al. 2003, Chun et al. 2006, Mariman & Wang 2010). In vivo, treatment of mice with factors that facilitate adipogenesis, such as rosiglitazone, or factors that suppress the inhibition of adipogenesis, such as TGFβ-neutralizing antibody, has shown success in reversing fibrosis in the skin (Du et al. 2013, Shi-wen et al. 2009). It will be important to better understand how adipocytes might acquire a myofibroblast phenotype in fibrosis and how their interactions with surrounding cell types might alter cell behavior to promote fibrosis.

Aging

Changes in adipose tissue occur during the aging process. vWAT increases whereas other depots, such as dWAT, shrink (Kuk et al. 2009, Tchkonia et al. 2010, Treiber et al. 2011). This decrease in the adiposity of the skin during aging may be related to the decreased capacity of APs to differentiate into mature adipocytes. APs isolated from human subjects can enter into a senescent state that impairs their ability to differentiate (Mitterberger et al. 2014). Recent research suggests that senescence of APs in WAT increases their expression of activin A, which is capable of inhibiting adipogenesis in neighboring APs (Xu et al. 2015). Determining whether senescence is a mechanism that regulates loss of adipose tissue in skin and elucidating whether there are changes in the numbers of APs that contribute to the diminished dWAT will be interesting future areas of investigation.

Cancer

Changes in the stromal macroenvironment can influence tumorigenesis and metastasis, yet exactly how these alterations contribute to tumor formation and progression is not well defined (Sleeman et al. 2012). Although adipocyte lineage cells are one of the most abundant lineages in skin, their involvement in skin cancer has not been examined. In other tissues, adipocytes contribute to tumorigenesis and protect tumor cells from treatments. Bone marrow–derived adipokine secretions have been implicated in the stimulation of metastatic prostate tumor growth and invasiveness (Herroon et al. 2013). When murine and human breast cancer cell lines were cocultured with mature adipocytes on transwells, the tumor cells showed greater invasion into matrigel and homing into mouse lungs after tail

vein injection. Interestingly, coculture with APs had no effect on tumor cell invasion. Subsequently, mature adipocytes decreased lipid storage and gene expression of adipocyte-specific genes while upregulating genes encoding inflammation-associated IL-6, IL-1β, CCL-2, CCL-5, and TNFα in response to coculture with cancer cell lines (Dirat et al. 2011, Picon-Ruiz et al. 2016). These findings highlight the bidirectional communication between adipocytes and cancer cells. The contribution of specific adipokines to cancer cell biology is just beginning to be examined (Giordano et al. 2015, Lee et al. 2016) and should provide significant insight into the molecular signaling between adipocytes and cancer cells. Recently, it was shown that preincubation of breast cancer cells with adipocytes increases cancer cell migration and resistance to trastuzumab treatment (Duong et al. 2015). A similar effect has been attributed to bone marrow adipocytes in myeloma chemotherapy resistance (Liu et al. 2015). Due to the decreased presence of dermal adipocytes in the stromal fraction of cutaneous tumors (Figure 3), many questions remain. Examining the fate of adipocytes, adipocyte lipid stores, and potential contributions of adipokines during tumor formation and metastasis will be an interesting area of investigation for future studies.

Obesity and Diabetes

Accumulation of WAT throughout the body during obesity is associated with many alterations in adipocyte physiology. In obese mice and humans, the balance of adipokine secretions is shifted toward an inflammatory state, and innate and adaptive immune cells become activated. Beneficial adipokines, such as adiponectin, are reduced, while cytokines that promote inflammation and insulin resistance, such as leptin and IL-6, increase (Frank et al. 2000, Guilherme et al. 2008, Ouchi et al. 2011, Wetzler et al. 2000). As systemic levels of beneficial adipokines decrease, the elevation of inflammatory cytokines creates low-grade inflammation in multiple organs, including the skin. Examination of serum adipokine levels in lean patients suffering from inflammatory diseases suggests that adipose tissue increases anti-inflammatory adipokine release in a putative attempt to dampen the immune response; however, in the obese state, anti-inflammatory adipokine levels are frequently decreased compared with lean, healthy baseline levels (Fantuzzi 2008). This observation demonstrates the systemic complexity associated with obesity and diabetes and helps to explain the high comorbidity of obesity and diabetes with inflammatory diseases.

Although the direct contribution of dWAT is unknown, obese individuals have a greater risk of acquiring many different cutaneous diseases, including ulceration, infection, and a diminished capacity to heal wounds (Frank et al. 2000, Guilherme et al. 2008, Shipman & Millington 2011, Yosipovitch et al. 2007). Relative to lean controls, obese women have a greater risk of *S. aureus* colonization (Olsen et al. 2013), and obese patients have a greater risk of infection after surgical procedures. Obese psoriatic patients are more likely to develop severe psoriatic outbreaks that are difficult to treat. As in other inflammatory diseases, the elevated inflammatory baseline associated with obesity is believed to contribute to activation of dendritic cells and T cells in psoriatic skin (Lowes et al. 2014). However, although the serum levels of many adipokines, such as adiponectin, leptin, and IL-6, are altered in psoriasis (Gerdes et al. 2011), there is little evidence to support that dWAT directly contributes to these altered serum levels.

Progression of obesity to type II diabetes is associated with insulin resistance and additional defects in skin biology (Guilherme et al. 2008). Altered insulin signaling leads to defects in human and mouse keratinocyte differentiation and migration in vitro (Benoliel et al. 1997, Wertheimer et al. 2000). Cell-intrinsic defects in keratinocytes may contribute to the inability of many diabetics to close skin wounds. Wound healing is significantly impaired in both diabetic patients and many animal models. Diabetic *ob/ob* and *db/db* mice have slower healing rates and persisting inflammation. In *db/db* mice, the numbers of neutrophils and inflammatory macrophages remain elevated for up to 10 days after injury and γδT cells are dysfunctional (Frank et al. 2000, Goren et al. 2003, Mirza & Koh 2011, Taylor et al. 2011, Wetzler et al. 2000). Wound beds of diabetic mice also have diminished levels of keratinocyte growth factor and acidic and basic FGF during the tissue formation phase of wound healing (Werner et al. 1994).

In addition to showing defects in keratinocyte function during diabetic murine wound healing, fibroblasts generate less collagen, resulting in both decreased tensile strength and decreased wound closure (Enser & Avery 1984, Goodson & Hunt 1979). Interestingly, human dermal fibroblasts cultured with high levels of leptin increased secretion of inflammatory cytokines (IL-6, CXCL-1, IL-8, and MCP-1), demonstrating that dermal fibroblasts may receive signals from adipose tissue and may contribute to a cutaneous inflammatory state (Ommen et al. 2015).

CONCLUDING REMARKS

Until recently, it was believed that WAT participated primarily in systemic metabolism and endocrine function. WAT is integrated into many mammalian tissues, and its expansion is associated with protective, regenerative, or pathological conditions. The diverse beneficial and deleterious contributions of WAT to tissue physiology make WAT an exciting and powerful target for translational biology. Over the past few years, many new mouse models have been developed to study mature adipocytes and APs in vivo (Jiang et al. 2014, Sassmann et al. 2010, Wang et al. 2013). It will be exciting to see these models implemented to selectively examine the function of WAT in skin, muscle, MG, and bone marrow and to determine how fat contributes to maintenance of these tissues and to the development of human diseases.

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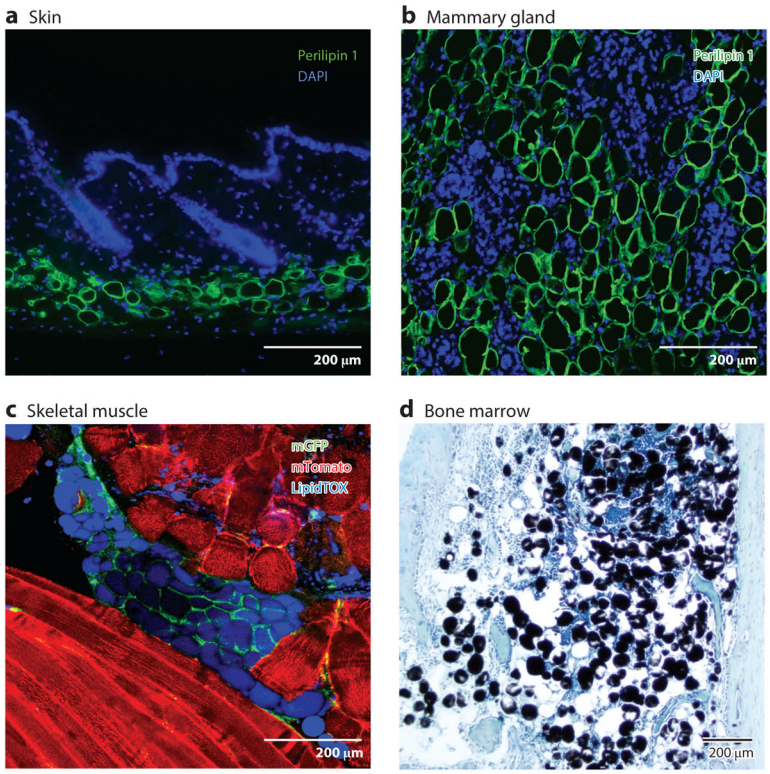

Figure 1.

White adipocytes reside in multiple tissues. (*a*) In skin, small perilipin 1–positive adipocytes are located in the deepest layer of the dermis. (*b*) Perilipin 1–positive adipocytes are found within the mammary gland stroma. The images show mouse mammary glands after 7 days after involution. (*c*) Lipid-filled mature adipocytes (LipidTOX positive) are present in skeletal muscle following injury. These cells are lineage traced from adipocyte precursor cells by crossing *Pdgfra*Cre with an mTomato/mGFP (membrane tomato/membrane GFP) reporter mouse. mGFP indicates lineage tracing. (*d)* Bone marrow adipose tissue expands in response to many diseases. Adipocytes in bone marrow are stained black by using osmium, and tissue is stained with toluidine blue. Images courtesy of Dr. Matthew Rodeheffer (panel *c*) and Dr. Mark Horowitz (panel *d)*.

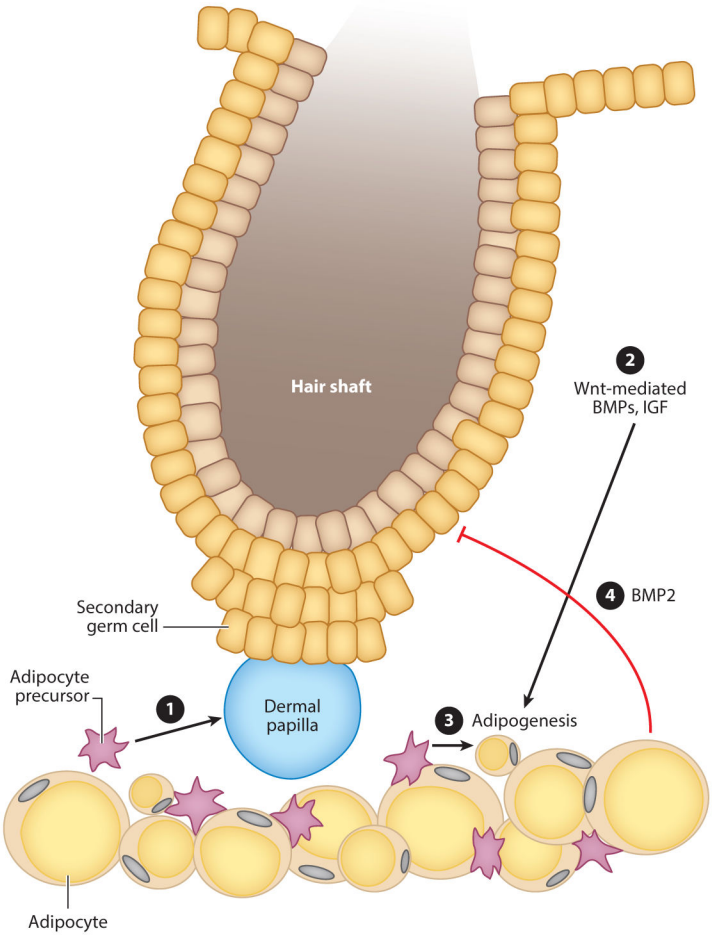

Figure 2.

Interaction between dermal white adipose tissue (dWAT) and hair follicle cycling. Hair follicles undergo cyclic growth (anagen), regression (catagen), and rest (telogen). ❶ During the telogen stage, signaling from adipocyte precursor cells (APs) activates hair follicle growth. ❷, ❸ Adipogenic factors are released by keratinocytes downstream of Wnt/β-catenin signaling, resulting in expansion of dWAT. Adipocyte size continues to increase during anagen. ❹ Adipocytes express high levels of BMP2 during late catagen/early telogen; BMP2 maintains the hair follicle in a resting state. Proliferation leads to AP pool expansion during this stage of the hair follicle cycle.

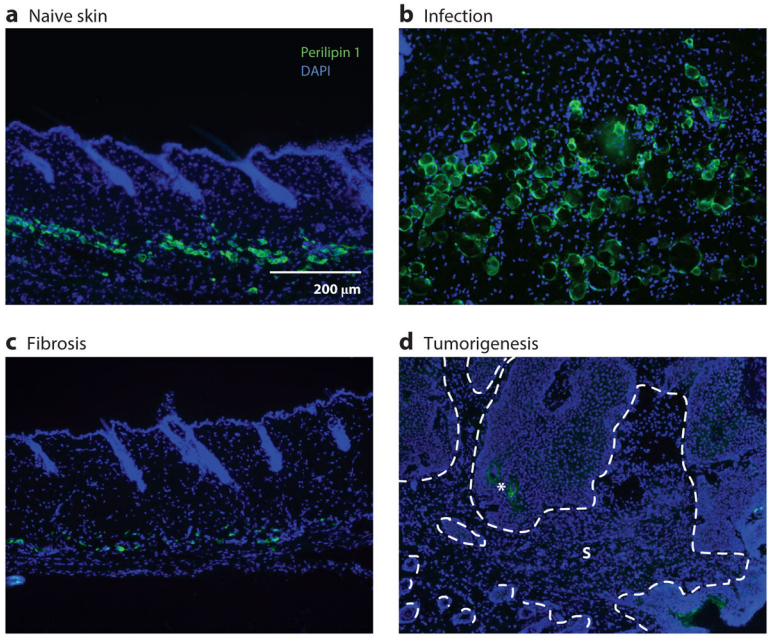

Figure 3.

Dermal white adipose tissue (dWAT) mature adipocytes are altered during cutaneous disease. (*a*) In naive skin in the rest stage of the hair cycle, small perilipin 1–positive mature adipocytes reside deep in the dermis. (*b*) Three days after infection of mouse skin with subcutaneous injections of *Staphylococcus aureus*, dWAT undergoes a dramatic expansion. (*c*) During bleomycin-induced skin fibrosis in mice, perilipin 1–positive cells become depleted. (*d)* Perilipin 1–positive adipocytes are absent from the stromal compartment of TPA/DMBA-induced skin tumors. The dotted lines denote the epithelial-stroma (S) border. The asterisk indicates autofluorescence. Image in panel *b* courtesy of Dr. Richard Gallo and Dr. Ling-juan Zhang.