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Viewpoint

Unravelling hair follicle–adipocyte communication

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Abstract: Here, we explore the established and potential roles for intradermal adipose tissue in communication with hair follicle biology. The hair follicle delves deep into the rich dermal macroenvironment as it grows to maturity where it is surrounded by large lipid-filled adipocytes. Intradermal adipocytes regenerate with faster kinetics than other adipose tissue depots and in parallel with the hair cycle, suggesting an interplay exists between hair follicle cells and adipocytes. While adipocytes have well-established roles in metabolism and energy storage, until recently, they were overlooked as niche cells that provide important growth signals to neighbouring skin cells. We discuss recent data supporting adipocytes as niche cells for the skin and skin pathologies that may be related to alterations in skin adipose tissue defects.

Key words: adipocyte – hair follicle – hypodermis – preadipocytes – skin – subcutis

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Scope

White adipocytes compose a major component of the skin, yet their role in skin biology has largely been ignored. This viewpoint article aims to discuss and speculate on potential roles of intradermal adipocytes in cutaneous biology with an emphasis on communication during hair follicle growth and regeneration. We discuss the organization of adipose tissue associated with the skin and describe how the size of this specialized adipocyte layer is regulated in parallel with the hair follicle cycle. We emphasize the potential role of adipocytes in hair growth and explore how alterations in the intradermal adipose tissue may support clinical manifestations of alopecia and hypertrichosis.

Cutaneous adipocytes: intradermal and subcutaneous depots

White adipose tissue (WAT) is composed of unilocular cells that function to store energy through their ability to accumulate and release fatty acids. While the mature adipocytes comprise the majority of WAT mass, WAT also contains several other cell types including immature adipocyte lineage precursors, blood cells, macrophages and endothelial cells (1,2). In addition to energy storage, WAT also has endocrine functions that are involved in food intake, glucose homoeostasis, lipid metabolism, inflammation and angiogenesis. Adipose tissue also provides non-energetic functions such as thermal insulation and mechanical cushioning of the body.

White adipose tissue develops at several specific locations called depots that display distinct cellular and molecular characteristics (1,2). Two major adipocyte depots are the subcutaneous depot below the skin and the visceral depot within the abdominal cavity. Previously, the skin-associated WAT was described as being located below the dermis or skin in the hypodermis and subcutis, respectively. However, a WAT depot exists below the reticular dermis in the skin and is clearly separated from the subcutaneous WAT depot in rodents by a striated muscle, the panniculus carnosus (Fig. 1). The majority of the human body lacks the panniculus carnosus, and yet, two histologically and anatomically distinct layers of adipose tissue exist under the reticular dermis (3–6). The most superficial adipocyte layer in human skin is morphologically and metabolically distinct from the deeper adipocyte layer. We refer to the upper layer of adipose as the 'intradermal' WAT depot because this layer surrounds hair follicles in both humans and rodents. This terminology ensures that the entire mature anagen hair follicle is included within the definition of the dermis and that the intradermal WAT depot is distinguished from the underlying 'subcutaneous' adipose tissue.

The murine intradermal adipocyte depot forms postnatally, resulting in a direct interaction of the growing hair follicles with adipocytes, a relationship reminiscent to the mammary gland epithelium, which grows and branches within a WAT depot (7). The organization of the intradermal WAT varies among different mammals from a continuous layer of adipocytes to a discontinuous layer of small adipocyte clusters specifically around compound hair follicles (8–10). During follicular morphogenesis, intradermal adipocytes form and grow via lipogenesis resulting in adipocyte hypertrophy and the formation of the intradermal adipocytes that surround each hair follicle. The mechanisms that induce intradermal adipocyte formation are not known.

The hair follicles of the skin continuously cycle through stages of growth and activation (anagen), regression (catagen) and quiescence (telogen). The hair follicle contains a unique population of stem cells that are located in a specific niche known as the bulge. During skin homoeostasis, the stem cells of the bulge are quiescent and become activated to initiate a new anagen phase (11). The dermal environment that surrounds each hair follicle is rich in multiple cell types including intradermal white adipocytes, dermal fibroblasts, smooth muscle and endothelial cells of the vasculature, neurons, smooth muscle cells of the arrector pili muscle, and resident immune cells. Recent data suggest that multiple cell types in the dermal macroenvironment are important in the maintenance of the bulge cell population and hair follicle growth (9,12,13). Here, we focus on the interplay between adipocytes within the skin, which have become an interesting topic of study, as recent research has shown that adipocytes have intriguing regulatory properties during hair follicle homoeostasis.

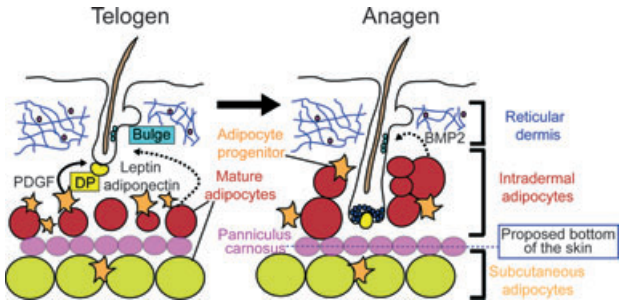

Figure 1. Model for potential roles of intradermal adipocytes in the regulation of hair follicle cycling. A distinct intradermal adipocyte layer exists in the skin, which underlies the fibroblast and extracellular matrix-rich reticular dermis and lies above the panniculus carnosus in rodents and the subcutaneous adipocytes. During the transition of the hair follicle from rest (telogen) to growth (anagen), adipocyte progenitor cells are activated to proliferate and form new mature adipocytes that surround the new hair follicle. These immature adipocytes express platelet-derived growth factor (PDGF), which can signal to activate anagen. Mature adipocytes also express leptin, adiponectin and BMP2, which may facilitate hair growth. Dotted lines indicate potential interactions that have not yet been shown conclusively.

In general, adipose tissue is long-lived, as adipocytes are estimated to persist in humans for 10 years (14). Early histological studies of the skin demonstrated that the layer of intradermal adipocytes expands as the hair follicle enters its growth stage and then thins during telogen (8,10,15–17). As mitotic nuclei were not identified by the histological methods of the time, it was hypothesized that hypertrophy was the primary mode of thickening during this hair growth transition. Indeed, hypertrophy of individual adipocytes does occur in the skin (7). However, the growth of the adipocyte layer during anagen induction also occurs through proliferation and differentiation of resident adipocyte precursor cells (7,18). Together, these data support the ability of intradermal adipocytes to form a thick depot through both adipogenesis and hypertrophy.

Hair growth in mice with abnormal adipocyte or sebocyte formation

Mouse models with defects in intradermal adipocytes have been reported. For instance, transgenic mice overexpressing human apolipoprotein C-I in the skin (19), fatty acid transport protein (*FATP*)-4-deficient mice (20) and *Dgat1*$^{-/-}$ or *Dgat2*$^{-/-}$ mice (21,22) have decreased intradermal adipose tissue owing to defects in lipid accumulation in mature adipocytes (Table 1). Interestingly, these mice also display abnormalities in skin structure and function such as hair loss and epidermal hyperplasia. However, these mutations also result in abnormal sebaceous gland function owing to the role of these proteins in sebaceous gland differentiation.

Several parallels exist between adipogenesis and sebocyte differentiation. Specification of the sebaceous gland first becomes evident postnatally with the identification of cells in the upper hair follicle that express the adipogenic transcription factor PPARγ (23). Further maturation of sebocytes results in large differentiated cells that are filled with lipids. Given that both adipocytes and sebocytes mature through PPARγ and lipid accumulation, variations in multiple genes that modify adipocytes may also affect sebaceous gland function. As defective sebaceous glands can change hair follicle stem cell activity and lead to skin abnormalities (23,24), the skin defects in the apolipoprotein C-I transgenic, *FATP4*$^{-/-}$, *Dgat1*$^{-/}$or *Dgat2*$^{-/-}$ mice were not clearly attributable to deficiencies in adipocytes in the skin but could be due to defects in sebocytes.

In contrast to the mouse models described above, several mutant mice with defects in adipocytes, but not sebocytes, have allowed the elucidation of the roles of adipocytes in the skin (11) (Table 1). A genetic mouse model lacking *Early B-cell factor 1* (*Ebf1*$^{-/-}$), which is expressed in the skin in intradermal adipocytes, sebaceous glands and dermal papillae of anagen hair follicles, exhibits reduced intradermal adipocytes (25) due in part to a lack of adipocyte precursor cells postnatally. Hair follicles in these mice also fail to re-enter anagen and instead remain in late catagen or telogen, which indicates the failure of bulge SC to become active following initial hair follicle growth.

The importance of immature adipocytes in the promotion of the telogen to anagen transition during the hair follicle cycle is clearly evident when these findings are compared to the AZIP mouse model. AZIP mice lack mature fat cells throughout the body, although these mice do have resident, and even elevated, numbers of intradermal adipocyte progenitor cells. The absence of mature adipocytes is attributed to the expression of a dominant-negative form of *C/EBP* in the late stages of adipogenesis, which blocks mature adipocyte formation (7,26). The hair follicles of these mice enter anagen at the same rate as wild-type mice.

Table 1. Mouse models with adipocyte and skin defects

Mouse line	Adipose defects	Skin defects	Reference
Early B-cell factor-1 (Ebf1$^{-/-}$*)*	Reduced intradermal adipocytes, lack of adipocyte progenitors in postnatal skin, increased number of bone marrow and liver adipocytes	Hair follicles fail to re-enter anagen	Hesslein *et al.* (25)
AZIP	Lack of subcutaneous and visceral WAT, decreased BAT, elevated numbers of adipocyte progenitors in putative visceral fat pad and skin	None reported	Moitra *et al.* (26), Rodeheffer *et al.* (18) and Festa *et al.* (7)
Waved-5 (*EGFR*$^{-/-}$)	Reduced intradermal adipocytes	Delayed entry into anagen	Maklad *et al.* (40) and Sugawara *et al.* (39)
Agpat6–/–	Reduced intradermal adipose tissue in adult mice	None reported	Vergnes *et al.* (63)
Fatp4–/–	Low body weight, reduced intradermal adipose tissue	Epidermal barrier defects, compact dermis, reduced number of sebaceous glands	Herrmann *et al.* (20)
Dgat1–/–, Dgat2–/–	Lack of ability to store triglycerides (*Dgat2–/–*)	Hair loss at 7 weeks, atrophic sebaceous glands at 3 months	Chen *et al.* (21) and Stone *et al.* (22)
APOC1	Lack of subcutaneous fat, reduced visceral adipose tissue	Scaly skin, loss of hair, atrophic sebaceous glands	Jong *et al.* (19)

WAT, white adipose tissue.

In addition to the requirement of adipocytes in the skin for anagen induction, adipocyte lineage cells are sufficient to induce the hair follicle cycle. Transplantation of adipocyte progenitor cells intradermally into the back skin of shaved mice at the extended 3–4 week telogen stage of the hair follicle cycle that occurs around 7 weeks of age resulted in adipocyte graft formation and corresponding precocious hair growth. Anagen was induced in these mice injected with the enriched adipocyte progenitor cells from WT or AZIP, but not with cells of the entire stromal vascular fraction (SVF), supporting that the hair-inducing activity was specific for immature adipocyte lineage cells (7).

The mechanism behind this interaction is not completely understood, but PDGF signalling may play a role (7). *PDGFA* mRNA is significantly elevated in adipocyte precursor cells, and mice lacking *PDGFA* show a delay in hair follicle stem cell activation that mirrors the phenotype of *Ebf1*$^{-/-}$ mice (27,28). The lack of mouse models that allow genetic manipulation in immature adipocytes to date precludes the specific genetic deletion of PDGF in intradermal adipocyte precursor cells. Future experiments can clarify the role of secreted factors produced by adipocytes during the hair cycle using engraftment of adipocyte lineage cells isolated from mice lacking specific factors.

In addition to adipocyte-derived induction mechanisms for hair growth, intrinsic mechanisms within hair follicles can activate the telogen to anagen transition (29). For instance, activation of calcineurin/NFAT signalling or hair plucking can induce hair cycling independent from adipogenesis (29–32). Whether hair activation can induce adipogenesis has not been explored. In addition, vibrissae hair follicles reside within an encapsulated blood sinus that lacks differentiated adipocytes, yet can cycle very fast and efficiently. Whether immature adipocytes or another cell type within the sinus promote the telogen to anagen transition is not clear.

Factors secreted from mature adipocytes may influence hair growth

Mature adipocytes also express signalling molecules that can modulate hair cycling. Intradermal adipocytes express *BMP2* maximally in late anagen and early telogen, causing follicles to be refractory to activation cues (30). Given that BMP signalling blocks anagen induction (33–36), these data suggest that adipocyte-derived BMPs may promote and maintain follicular stem cell quiescence. Thus, when BMP signals are reduced in the macroenvironment, the hair follicles are open to activation signals, enter into a competent telogen phase and the follicles can re-enter anagen. The contribution of adipocyte-derived BMP proteins is unknown because the dermal papillae also express *BMP* mRNAs (37).

Epidermal growth factor (EGF) signalling may be another possible connection between the hair follicle and intradermal adipocytes. Mutations in the EGF receptor that result in the expression of a dominant-negative EGFR (38) cause a slightly delayed regression of the follicle during catagen, as well as a wavy hair phenotype. Interestingly, during early postnatal stages, the intradermal adipocyte layer is reduced during the initial stages of anagen (39). As mice that conditionally lack *EGFR* in the skin epithelium also display defects in intradermal adipocytes (40), the hair follicle may regulate intradermal adipocyte growth in signalling pathways downstream of EGFR or through the hair follicle cycle itself. Future work will be needed to tease out the interplay between the hair follicles and intradermal adipogenesis.

The expression of classic adipokines and long-chain free fatty acids (FFAs) may also impact hair follicle biology. The leptin receptor is expressed on dermal papillae cells (41). In addition, adiponectin has been shown to influence keratinocyte growth and differentiation (42). In addition to functioning as energy sources, long-chain fatty acids have been recognized as crucial elements of signalling pathways, particularly those involved in the endocrine, nervous and immune systems (4,43,44). FFAs can act as secondary messengers and ligands to act both intra- and intercellularly to elicit or amplify metabolic responses (45–47). FFAs, particularly oleic and palmitic acids, have been shown to regulate gene expression at the transcriptional level in adipocytes (48–50). FFA have additionally been shown to reduce dermal fibroblast proliferation (51). Adipose tissue is the source of most FFA found systemically, and alterations in lipid metabolism can affect the amount of FFA found throughout the body (52). Excess FFA, such as in cases of obesity, can result in altered metabolic function of numerous body organs, including, but not limited to, the liver, heart and skeletal muscle. It is possible that FFA and other adipokines in the skin also have similar functions and may directly or indirectly contribute to gene or protein expression in the hair follicle or appendages. The possibility that these molecules are 'feeding' or signalling to the hair follicle cells has not yet been explored. AZIP mice may be useful to tease out the impact of mature adipocytes on the homoeostasis of the skin.

Potential cutaneous manifestations of lipid-associated diseases in humans

Extrinsic regulation of the hair follicle cells from the macroenvironment has the potential to alter the clinical perspective of disorders affecting human hair follicle biology. Several disorders are known to increase or involve an absence of fat mass including obesity and lipodystrophy, respectively, and intradermal adipocytes are clearly becoming recognized for more than just their roles in energy storage (53). Lipodystrophy can be associated with alopecia (54,55) and hirsutism (56). In addition, production of certain adipokines, such as leptin, adiponectin and visfatin is increased in patients with psoriasis (57). Furthermore, patients with Goltz syndrome or focal dermal hypoplasia display alterations in skin adipose tissue associated with sparse, brittle hair with patchy alopecia (17,58). Obesity can also be associated with hirsutism and hypertrichosis, or excessive hair in areas that are not usually androgen responsive (59). Interestingly, mice lacking androgen receptor (AR) become obese suggesting a link between androgen signalling and adipocytes (60). Furthermore, expression of AR has also been shown *in vitro* to downregulate the expression of PPARγ mRNA (61), as well as to reduce the proliferation of adipocyte progenitors (62). As dysfunction of adipocytes can alter insulin signalling and other metabolic signalling pathways, establishing the role of intradermal adipocytes in many of these disorders may alter treatment options for cutaneous manifestations of these diseases.

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Conflict of interests

The authors have declared no conflicting interests.

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