Letter to the Editor

Stem Cell INVESTIGATION

PDGFA regulation of dermal adipocyte stem cells

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Provenance: This is an invited Letter to the Editor commissioned by Editor-in-Chief Zhizhuang Joe Zhao (Pathology Graduate Program, University of Oklahoma Health Sciences Center, Oklahoma City, USA).

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Adipose tissue is widely studied for its central role in regulating systemic metabolism and contribution to obesity-related diseases; however, skin resident dermal white adipose tissue (dWAT) also contributes to many aspects of skin function. Skin-resident mature adipocytes are thought to prevent hair growth activation through the secretion of BMP molecules (1). Furthermore, following *S. aureus* infection, adipose tissue in the skin expands and produces an antibacterial peptide (2). During wound healing, defects in adipogenesis can abrogate fibroblast recruitment into wound beds, leading to defects in extracellular matrix deposition and tissue repair (3). Migration of adipocyte precursors into the wounded area might also contribute to the mesenchymal repopulation of the wounded site (4) and in wounds where hair follicle neogenesis is observed fully functional adipocyte precursors are present (5). These findings highlight the breadth of the role of adipose tissue in the skin.

Another remarkable aspect of adipose tissue in the skin is its dynamic regenerative cycles that parallel the hair cycle (6). The expansion of dWAT during hair growth occurs through activation of adipocyte precursors that have been identified in other tissues as adipocyte stem cells (ASCs) and enlargement of existing mature adipocytes (6,7). Recent work from our group revealed a role for PDGF signaling in maintaining a sub-population of ASCs (8). Some of these findings have been recently discussed by two editorials from Cappellano & Ploner (9) and Dani & Pfeifer (10). These editorials raise interesting questions regarding how our findings connect with previous research in skin and other tissues. Here, we contribute to this discussion of dWAT regulation and complexity underlying PDGF signaling.

ASCs in the skin that lack PDGFRα expression are not maintained and PDGFA treatment of adipocyte precursors (ASCs and pre-adipocytes) *in vitro* results in expression of pro-proliferative genes through activation of the PI3K/AKT pathway. Diminished dWAT and low numbers of ASCs in aged wild-type and Pdgfa cKO mice indicates that PDGF signaling is important for normal adipose tissue maintenance in skin. In order to understand how dWAT is maintained, unique environmental factors must be uncovered. Our research revealed that PDGF signaling is important for maintaining dWAT ASCs. We also examined the numbers of ASCs from perigonadal and inguinal white adipose tissue in *Pdgfa* cKO mice and failed to observe changes in ASC numbers (8).

One possibility mentioned by Cappellano & Ploner is that distinct environmental mechanisms might operate in different fat depots (9). This interesting possibility ties into the important role of the environment in adipocyte precursor activation and new mature adipocyte formation during high-fat diet feeding in inguinal and perigonadal fat (11). Local interactions with skin-resident mesenchymal or epithelial cells could prime ASCs in the skin to proliferate in response to PDGFA (12,13), while the lack of these cells in perigonadal and subcutaneous adipose tissue might contribute to depot specific differences. Another explanation could be the accelerated rate of adipocyte generation displayed by skin. Skin generates new adipocytes during the transition from the quiescent phase (telogen) to the growth phase (anagen) of the hair follicle cycle in as little as 2 weeks (6,8). Generation of adipose tissue in the

inguinal and perigonadal fat depots takes approximately 8 weeks during high fat dieting (14). The rapid transition from precursor to adipocyte in the skin suggests that either dWAT precursors or environmental factors differ dramatically from other adipose depots or that while regulation might be similar between different depots, the time frame in which biological processes happen greatly differ between individual depots. To investigate whether dermal environmental factors influence ASC differentiation state, further experimentation could evaluate the ability of ASCs from perigonadal and subcutaneous fat depots to be maintained in skin in the absence of PDGFRα signaling using a cell transplant approach or in their adipose tissue of origin over longer periods of time.

A link between ASCs and PDGF signaling during wound healing and scarring was another interesting possibility raised by the Cappellano & Ploner comment (9). A recent study identified that young but not aged inguinal mesenchymal cells, including adipocyte precursors, have a positive effect on wound closure and vascularization during dermal wound healing (15). Our work identifying a loss of ASCs during aging in the skin suggests that loss of adipocyte precursors during aging might contribute to this loss of healing potential. Interestingly, ASCs share multiple molecular markers with wound bed fibroblasts (PDGFRα, Sca1, CD34) (4,16), suggesting adipocyte precursors give rise to cells that actively contribute to skin repair. Further experiments are needed to clarify the potential of adipocyte progenitors to generate or act as fibrogenic cells, similar to fibro-adipogenic progenitors in skeletal muscle (17), or whether adipocyte precursors are a heterogeneous population with some cells able to become adipogenic while others might contribute to the wound healing process. Evidence for adipocyte precursor heterogeneity can be found in a recent study where CD9 was found to distinguish two mesenchymal cell types in adipose depots. Within the adipocyte precursor population, $CD9^{high}$ cells generated fibroblasts whereas $CD9^{low}$ progenitors were transcriptionally committed to the adipose lineage (18). A more comprehensive understanding of mesenchymal heterogeneity in wounded and unwounded skin will allow researchers to better define the lineage relationships between dermal cells and target specific cellular subsets and signaling pathways that could selectively activate specific "fibroblast" subsets to impact dermal healing and scarring.

The final point that was highlighted by Dani & Pfeifer was the complexity of PDGF signaling that may contribute to the regulation of adipocyte precursor cells (10). The authors discuss two observed effects from the stimulation of PDGFR in adipose progenitors. Our study showed that decreased PDGFRα signaling leads to a loss of ASCs (8), while a prior study showed that an expression of a constitutively active PDGFRα mutant in mesenchymal cells leads to fibrosis (19,20). It is possible that the level of receptor activation might determine whether the biological response will be maintenance of ASCs or induction of fibrosis. The physiological context of the tissue might also contribute to the outcome of PDGFRα activation, for example during homeostasis, PDGFRα activation could promote ASC maintenance while in an environment where acute or chronic inflammation is present, PDGFRα signaling could promote a fibrogenic phenotype. Therefore, understanding whether signals in the environment or the length and/or strength of PDGFRα stimulation can modulate the biological response of ASCs and fibroblasts will be of great importance to the development of PDGF-based therapies for the improvement of wound healing and fibrosis.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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