Editorial

Stem Cell INVESTIGATION

Dermal white adipose tissue renewal is regulated by the PDGFA/AKT axis

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Disesteemed for many years as tissue exclusively dedicated to energy storage, the white adipose tissue (WAT) has become one of the most studied tissues, especially as recent reports uncovered its metabolic and endocrine functions *in vivo* contributing to the development of metabolic disorders, control of immune response and wound healing processes. The traditional classification of WAT describes two distinct anatomical depots, namely subcutaneous WAT (sWAT) and visceral WAT (vWAT), which exhibit differences at the cellular level and in structure (1). These differences may also be responsible for depot-specific WAT function and affect tissue plasticity and remodeling. More recently, a third type of WAT, which is referred to as dermal WAT (dWAT), received high appreciation, as it was identified as central contributor in skin-relevant processes including hair follicle growth, thermoregulation and wound healing (1). In contrast to long-lived adipocytes in sWAT and vWAT-depots, dWAT is characterized by rapid adipocyte turnover, adipocyte-myofibroblast plasticity and depot-specific cytokine profiles that have an impact on the differentiation and self-renewal abilities of skin regenerative cells, especially hair follicle stem cells. Due to these specificities, self-renewal of adipocyte progenitor cells and regulation of tissue homeostasis in dWAT is suggested to be differentially regulated compared to the other WAT depots. To address this issue Rivera-Gonzales *et al.* (2) established a mouse model to investigate the molecular mechanisms specifically regulating tissue homeostasis in dWAT.

Exploiting this model, they identified the PDGFA/AKT2 axis as a potential regulator of self-renewal in Lin(–):CD29(+):CD34(+):Sca1(+):CD24(+) adipocyte progenitor cells (CD24+ ASC) (2), which represent a subpopulation of the WAT stromal vascular fraction (SVF), capable of generating functional WAT *in vivo* (3). Interestingly, CD24+ ASC numbers decreased with age and proliferation of this cell population was sensitive to the expression of PDGFA, since lack of PDGFA reduced numbers of CD24+ ASC. This effect was specific to dWAT, as CD24+ ASC numbers remained constant in other WAT-depots suggesting additional regulatory mechanisms controlling self-renewal in these WAT-types. This finding is of great interest, as it suggests distinct environmental mechanisms may operate in different WAT depots that not only rely on the steady-state levels but are also differentially influenced by exogenous factors such as obesity, cold or aging.

With regards to speculating which environmental factors specifically drive CD24+ ASC renewal in dWAT, but have less influence on the repopulation of sWAT or vWAT regenerative cells, anatomical demarcation of dWAT might give some possible hints. Embedded between skin dermis and the panniculus carnosus in rodents (4), dWAT is constitutively exposed to physical stress, applied as shear stress or physical pressure that implies phenotypic flexibility and high turnover rates to maintain tissue homeostasis. These mechanical cues are transmitted to the nucleus by mechano-sensitive pathways (e.g., the Hippo-

Pathway), which in turn control factors involved in the regulation of adipogenesis (5). Mechanical stimulation induces continuous readaptation of the extracellular matrix building up the cellular homing niche, which in addition to cytokine-signaling regulates ASC fate through integrin signaling (6). Of note, studies investigating the effect of shear fluid stress on paracrine function of vascular endothelial cells, showed that PDGFA and PDGFB levels increased upon mechanical stimulation in an NF-κB dependent manner (7). Interestingly, this type of stimulation also influenced the adipogenic properties in human mesenchymal stem cells (8). Both studies indicated that in addition to the proposed PI3K/AKT2 activated pathway upon PDGFA/PDFGRα stimulation, mechanical stimulation may be a trigger for dWAT precursor cells to undergo proliferation and/or lineage commitment and differentiation.

Unlike the murine dWAT, which represents an individual layer separated from sWAT by the panniculus carnosus, human dWAT is organized in cone-like structures localized proximal to pilosebaceous units including hair follicles and sebaceous glands (1). Interestingly, in humans the cone-like dWAT structures are only present in body areas that are prone to scarring (e.g., abdomen, neck, chest, etc.) and are not pronounced in areas associated with reduced scarring such as scalp, forehead or early fetus (9). These observations further support the importance of dWAT in the wound healing process and suggest a connection between dWAT and scarring in human. Thus it would be interesting to address as to whether/how molecular mechanisms regulating CD24+ ASC self-renewal as shown by Rivera-Gonzales *et al.* (2), also contribute to dermal wound healing and scarring. Of note, a study investigating the effects of ASC on dermal wound healing in mice has already demonstrated that transplantation of ASC harvested from young mice improved wound healing in aged mice (10). Interestingly, the pro-healing effects were not observed if ASC from aged mice and failed to enhance wound healing rates. The authors of this study postulated that this effect was due to a depletion of a functional subset of ASC expressing anti-oxidative and pro-regenerative cytokines (10). Thus, decreased levels of PDGFA and thus reduced CD24+ASC numbers in aged mice might define the mechanism underlying this observation.

The specificity of discrete WAT-depots requires a focused consideration of each single adipose tissue type. Rivera-Gonzales *et al.* have provided new insights into the regulation of dWAT tissue homeostasis and identified a depot-specific molecular mechanism regulating self-renewal of dWAT regenerative cells in a mouse model. It remains to be proven if those mechanisms are also responsible for regulation of human dWAT tissue homeostasis and whether these findings may contribute to explain the role of dWAT in wound healing and scarring.

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Footnote

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