ADIPOSE TISSUE

Stem cells define adipose depot differences

> ASC heterogeneity in different white adipose tissue depots is important for distinct features of these depots

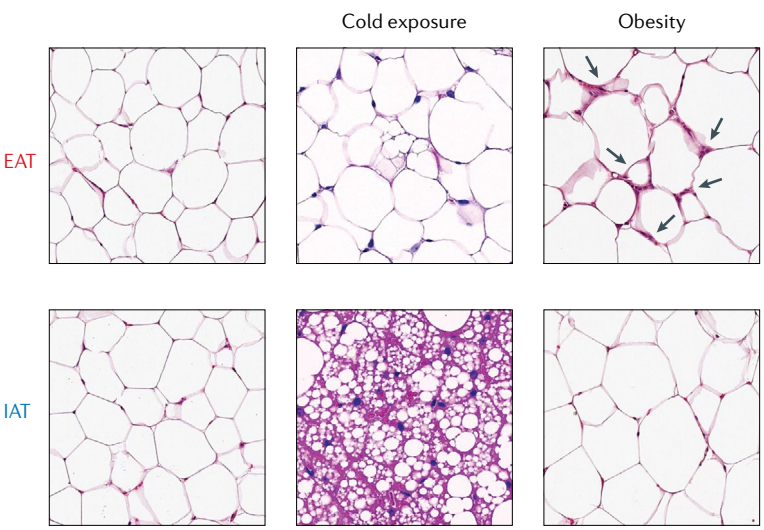
Visceral epididymal adipose tissue (EAT) and subcutaneous inguinal adipose tissue (IAT) are two important white adipose depots found in mammals that have distinct metabolic properties. Previous work suggests that subpopulations of adipose stem cells (ASCs) could explain functional differences in adipose depots; however, ASCs of EAT and IAT have not been directly compared. A new study published in *Cell Metabolism* shows that distinct properties of ASC subpopulations define the characteristics of EAT and IAT.

"In the present study, we have comparatively investigated ASCs from two mouse white adipose depots through single-cell RNA sequencing," explains corresponding author Jae Bum Kim. "To identify adipose depot-specific ASC clusters, we adopted a projection analysis in which EAT ASCs could be projected onto similar IAT ASCs or vice versa." This approach enabled the researchers to create a detailed map of ASC clusters in mouse EAT and IAT.

Analysis of ASCs from mice fed a normal chow diet showed that both EAT and IAT ASC clusters divided into three adipogenic differentiation stages. In EAT, these were multipotent ASCs (ES1), early committed preadipocytes (ES2) and late committed preadipocytes (ES3). In IAT, the corresponding populations were IS1, IS2 and IS3. Of note, committed preadipocytes were more abundant in EAT than in IAT. However, gene expression profiles of the three different stage clusters were different between EAT and IAT ASCs. This finding implies that different subpopulations of EAT and IAT ASCs might have different biological properties.

Next, ASC transfer experiments in mice showed that cell-intrinsic features of ES1 and IS1 ASC populations drove cell commitment towards preadipocytes. The adipose tissue microenvironment seemed to have a marginal effect. Of note, suppression of *Wnt2* expression in IS1 ASCs increased cell lipid content and adipogenic marker gene expression. By contrast, *Wnt2* suppression in ES1 ASCs did not affect adipogenic potential. This finding suggests that WNT signalling in IS1 ASCs might prevent adipogenesis.

To examine the effects of obesogenic stimuli, mice were fed a high-fat diet (HFD) or a normal chow diet and ASC clusters were analysed. After a 3-day or 7-day HFD, the number of ES1 ASCs was increased in EAT; ES3 ASCs were sequentially expanded in number after a 10-week HFD. Investigation of potentially important receptor–ligand pairs showed that fibroblast growth factor and transforming growth factor β signalling might mediate the proliferation of ES1 ASCs after 3 days of HFD. In contrast to EAT, IAT showed no notable changes in proportions of IS1, IS2 or IS3 ASCs during HFD feeding.



Histological images of visceral epididymal adipose tissue (EAT) and subcutaneous inguinal adipose tissue (IAT) from control, cold-exposed and obese mice. Image courtesy of Jae Bum Kim/Seoul National University.

During obesity, EAT undergoes fibrosis and inflammation. An important finding in this study was that in HFD-fed mice, proinflammatory SDC1^{+} ASCs were differentiated in EAT but not in IAT, which could facilitate fibrosis. Furthermore, in HFD-fed mice, CXCL14^{+} ASCs in IAT were found to supress tissue infiltration by monocytes by inhibiting the CXCL12–CXCR4 axis. Thus, these distinct subpopulations of ASCs have important proinflammatory or anti-inflammatory roles in different adipose depots.

Previous work has suggested that beige adipocyte precursors might be different from classic white adipocyte precursors. Beige adipocytes are rarely observed in EAT, so a comparative analysis was carried out between EAT and IAT to identify specific beige adipocyte precursors in IAT. Interestingly, BST2^{high} ASCs were abundant in IAT and were very rare in EAT. Further experiments showed that upon cold exposure, IAT-specific BST2^{high} ASCs could differentiate into beige adipocytes. Lymph nodes are found in IAT and not in EAT, and the biogenesis of IAT-specific BST2^{high} ASCs was found to be regulated by lymph nodes.

In summary, ASC heterogeneity in different white adipose tissue depots is important for distinct features of these depots that influence systemic metabolism. "Our future studies will explore which factors determine the differentiation fate of adipose depot-specific ASC clusters," concludes corresponding author Jong Kyoung Kim. "Also, we plan to examine whether these adipose depot-specific ASCs are crucial for human metabolic diseases."

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