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Distinct adipocyte progenitor cells may reveal therapeutic strategies for obesity

Fat tissue is essential for the safe storage of excess calories and thereby plays a key role in metabolic health. By storing lipid droplets, fat cells (adipocytes) protect organs from the damaging effects of ectopic lipid accumulation (*1*). Understanding how to promote healthy fat expansion may therefore reveal treatments for obesity and related diseases. Such expansion depends on the formation of new adipocytes from progenitor cells within fat tissue (*2*). Distinct populations of adipocyte progenitor cells (APCs) have been identified, but their interrelationships and relevance to physiological and pathological fat expansion have remained poorly understood (*3*). On page 353 of this issue, Merrick *et al.* (*4*) identify three new classes of APCs that are regulated with obesity, one of which resides in a potential new stem cell niche for tissue regeneration and repair.

Deciphering APC biology is complicated by the heterogeneous nature of fat tissue. To isolate APCs from the fat of mice, Merrick *et al*. used a method called fluorescence-activated cell sorting (FACS), which separates fat cells based on the presence of specific cell-surface proteins. This cellular pool was further resolved using single-cell RNA sequencing (scRNAseq), allowing cells to be grouped on the basis of similarities in their gene expression. Most cells fell into one of three groups that had not been defined previously: interstitial progenitor cells (IPCs), defined by expression of a protein called dipeptidyl peptidase–4 (DPP4); preadipocytes, marked by expression of intercellular adhesion molecule–1 (ICAM1); and group 3 cells, which expressed the protein CD142 (see the figure). Each group formed adipocytes in cell culture, thus supporting their identification as APCs.

Different types of fat tissue, called depots, exist in distinct anatomical locations, with distinct cellular and functional characteristics and pathological implications (*2*). Do APC classes differ between depots? Merrick *et al*. found that visceral fat has fewer IPCs than subcutaneous fat, analogous to depot-dependent differences reported elsewhere (*5-9*). It remains unclear whether these APCs exist in other depots, such as bone marrow fat (*10*); however, they were also detected in brown fat, a depot that may help treat obesity.

To determine whether different APC classes interconvert in vivo, Merrick *et al*. obtained IPCs, preadipocytes, and group 3 cells from newborn mice genetically engineered to express a red fluorescent protein. This allowed the cells to be tracked after transplantation into normal newborn recipients. Doing so revealed that IPCs acted as progenitors for both ICAM1+ and CD142+ cells, which themselves interconverted in vivo but did not revert to IPCs. Each of these APC types also gave rise to adipocytes in vivo, further demonstrating their role in fat development. The use of newborn mice is notable: Other studies focused on adults only (*5, 7, 9, 10*), leaving the developmental relevance of the APCs studied unclear. By contrast, Merrick *et al*. identified IPCs, preadipocytes, and group 3 cells in adults and newborns, observing similar proportions at each age. This suggests that these APCs contribute not only to postnatal fat development but perhaps also to maintenance of fat tissue in adults. Analysis of adult APCs by scRNAseq and in vivo tracking could address this possibility.

What about the pathological relevance of the APC subtypes? Merrick *et al*. noted that in obese, glucose-intolerant mice, visceral fat had fewer IPCs and a greater proportion of group 3 cells, similar to what was found in previous reports about other APCs (*9*). However, they also found that in obesity, the ability of preadipocytes or group 3 cells to form adipocytes is enhanced in subcutaneous fat but impaired in visceral fat. Such differences might contribute to the different health implications of excessive visceral versus subcutaneous fat storage.

Merrick *et al*. used the same approach to study APCs in subcutaneous fat of humans. The authors identified two general classes of APCs, analogous to the IPCs and preadipocytes in mice; however, group 3 APCs were not detected. By contrast, another study defined CD142+ APCs as adipogenesis regulatory cells that exist in the fat of mice and humans, suppressing adipocyte formation in each species (*9*). Unlike Merrick *et al.*, this study analyzed human fat by FACS only. Thus, it seems likely that technical differences might underlie these inconsistencies.

A major challenge is that different studies classify APC subtypes based on distinct criteria, making it difficult to reach a consensus. The study of Merrick *et al*. directly compared the characteristics of the APCs they identified with those of other studies, demonstrating how their IPCs, preadipocytes, and group 3 cells overlap with other APC subtypes identified elsewhere (*5, 7, 9*). However, there is likely to be further heterogeneity among these APC classes, and other distinct subtypes may also exist. It would be helpful for the field to reach some consensus around the identities of such APC classes, the methods used to characterize them, and their existence in humans.

Many reports indicate that APCs reside near blood vessels (*2, 3*), but Merrick *et al*. noted that IPCs were found within the reticular interstitium, a fluid-filled network of collagen and elastin fibers that encases many organs. By contrast, preadipocytes were observed beyond the reticular interstitium, adjacent to adipocytes. Between the IPCs and preadipocytes were cells expressing both DPP4 and ICAM1, suggesting a transition from IPCs to preadipocytes. The presence of IPCs within the reticular interstitium was assessed only for subcutaneous fat of mice. Hence, it remains unclear if this represents a common site for IPCs among all fat depots, or if it is analogous to the mesothelium as a source for visceral fat progenitors (*6*). Whether the reticular interstitium plays a role in humans also remains to be determined. However, given that the reticular interstitium exists in multiple human tissues (*11*),, an intriguing possibility is that it represents a new stem cell niche for fat tissue and beyond.

Adipose formation and function are influenced by diverse physiological and pathological factors, including genetics, age, sex, ethnicity, diet, and many clinical conditions. What is the relationship between these factors, APC function, and the reticular interstitium? Moreover, some antidiabetic drugs can modulate APC dynamics (*12*), and DPP4 is a target of other antidiabetic therapies (*10*). Whether such treatments can influence the DPP4-expressing IPCs, or other APC subtypes, remains unknown.

A major challenge will be to determine the implications of altered APC function in health and disease. Doing so holds great promise: By further unraveling the mysteries of APC biology, we may ultimately be able to target these cells to improve human health.

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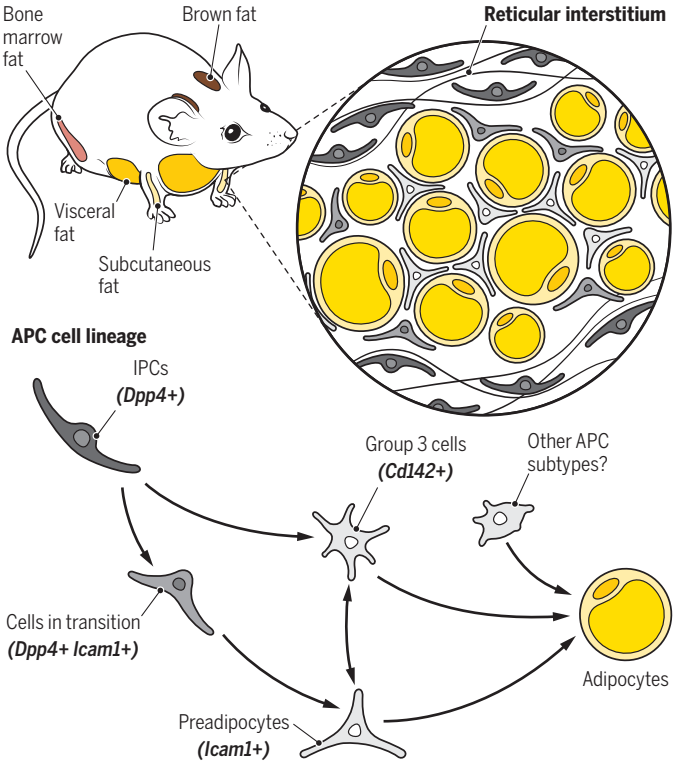

Figure 1 – Fat cell progenitors
Interstitial progenitor cells (IPCs), preadipocytes, and group 3 cells are adipocyte progenitor cells (APCs) that are present in different fat depots of mice. These cell types interconvert and are altered in obesity, highlighting potential physiological and pathological implications. IPCs in subcutaneous fat reside in the reticular interstitium, which might represent a new stem cell niche for fat cells.