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Two types of brown adipose tissue in humans

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During the last years the existence of metabolically active brown adipose tissue in adult humans has been widely accepted by the research community. Its unique ability to dissipate chemical energy stored in triglycerides as heat makes it an attractive target for new drugs against obesity and its related diseases. Hence the tissue is now subject to intense research, the hypothesis being that an expansion and/or activation of the tissue is associated with a healthy metabolic phenotype. Animal studies provide evidence for the existence of at least two types of brown adipocytes. Apart from the classical brown adipocyte that is found primarily in the interscapular region where it constitutes a thermogenic organ, a second type of brown adipocyte, the so-called beige adipocyte, can appear within white adipose tissue depots. The fact that the two cell types develop from different precursors suggests that they might be recruited and stimulated by different cues and therefore represent two distinct targets for therapeutic intervention. The aim of this commentary is to discuss recent work addressing the question whether also humans possess two types of brown adipocytes and to highlight some issues when looking for molecular markers for such cells.

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The existence and importance of active brown adipose tissue (BAT) in newborn humans has been recognized for many years.[1,2] However, until recently it was assumed that the tissue regresses and that functionally relevant BAT is essentially absent in adult humans.[3,4] An important observation that challenged this notion was made in the field of nuclear medicine.[5] When performing positron emission tomography with [^{18}F]-fluorodeoxyglucose for staging of cancer, a confounding symmetrical uptake of the tracer was found in neck and shoulder areas of patients. CT showed that these tumor-unrelated areas presented with features of adipose tissue. These findings triggered the initiation of several studies all dedicated to test the hypothesis that adult humans actually do have significant amounts of metabolically active BAT, and in April 2009 three independent studies demonstrating the presence of such tissue in adult humans were published in the *New England Journal of Medicine*.[6-8] Since then a large number of studies related to BAT in humans have been published and it is now a well-accepted fact that, not only human infants, but also a majority of adults possess metabolically active BAT.[9-12]

At least in rodents, an activation and/or expansion of BAT results in a metabolically beneficial phenotype with less obesity and increased insulin sensitivity.[13-16] Moreover, in humans the presence of BAT is inversely associated with obesity and type 2 diabetes mellitus.[6,12,17,18] It is now clear that rodents harbor at least two different types of brown adipocytes. Apart from the classical brown adipocytes that build up the thermogenic organ located in the interscapular area (iBAT), a second kind of brown adipocytes, so-called beige adipocytes (also referred to as brite adipocytes or inducible brown adipocytes) exist. These beige adipocytes typically appear within white adipose tissue (WAT), usually in the subcutaneous compartment, in response to cold or β3-adrenergic stimulation.[19,20] The two cell types are most likely

of different developmental origin since lineage tracing experiments have demonstrated that classical brown adipocytes, but not beige adipocytes, derive from precursor cells that express *Myf5*, a gene encoding a regulatory factor crucial for myogenesis and previously thought to be expressed only in cells giving raise to skeletal muscle.[21] Beige adipocytes on the other hand appear to develop from bipotential adipocyte progenitor cells resident in the perivascular region of WAT.[22] These cells that express PDGFRα, Sca-1, and CD34 have the potential to develop into beige adipocytes in response to β3-adrenergic stimulation. Interestingly, in response to a high fat diet such progenitors can also develop into white adipocytes. The notion that the classical brown and beige adipocytes seem to develop from different progenitor cells implies that they might respond differently to physiological and environmental cues and therefore represent two separate targets for pharmacological intervention.

It was recently suggested that the BAT identified in the supraclavicular area of adult humans was of the beige type and it was questioned whether humans possess classical brown adipocytes at all.[23-25] Two studies addressing this question were published in this year's May issue of *Nature Medicine*.[26,27] In the first study we used the fact that anatomic studies performed in the 1960s indicated the presence of BAT in the interscapular region of human infants; a location similar to the classical brown adipocyte containing iBAT of rodents.[27,28] We performed postmortem magnetic resonance imaging on eight human infants. Using the fat fraction method we identified potential iBAT, and from a subset of the subjects we obtained biopsies from the areas of interest. The histomorphology of the collected BAT closely resembled that of iBAT depots of rodents as it consisted of densely packed multilocular and UCP1-positive cells delineated from the subcutaneous WAT by a layer of connective tissue. In order to determine the classical brown or beige identity of the BAT cells we analyzed the expression of previously identified marker genes in the biopsies. Special care was taken to acquire a cell population as pure as possible and devoid of contaminating cell types from surrounding tissues such as WAT, skin, and skeletal muscle. Hence the biopsies were either dissected under a microscope or sectioned and subjected to laser capture microdissection. The gene expression signature of the isolated cells was then assessed by quantitative real-time PCR using published marker genes for classical brown and beige adipocytes, respectively. The gene expression profile was compared with that of samples obtained from two other BAT depots; supraclavicular BAT from healthy adult subjects and periadrenal BAT isolated from patients undergoing surgery for benign adrenal tumors. BAT sampled from the interscapular area expressed significantly higher levels of *ZIC1*, a gene which was previously suggested to be the gene that best discriminates between iBAT and beige BAT in mice.[29] Using clonal cell lines established from stromal vascular fractions of inguinal subcutaneous fat and of iBAT, Wu et al. reported *Tbx1* to be preferentially expressed in beige as compared with classical brown adipocytes.[24] This beige-selective gene was also used when classifying human supraclavicular BAT as being a beige depot.[24] We demonstrated that this beige-selective marker was expressed at a significantly lower level in the BAT sampled from the interscapular area as compared with in the presumably beige subcutaneous supraclavicular BAT. Taken together, our data suggest that human infants, like rodents, possess bona fide iBAT containing classical brown adipocytes and that humans actually do have two types of brown adipocytes.

In the second *Nature Medicine* article, Cypess et al. deciphered the anatomical location and gene expression of neck BAT from patients undergoing anterior cervical spine surgery or thyroidectomies.[26] They concluded that the adipose tissue changed its histological and ultrastructural features from the superficial to deeper compartments; the superficial adipose tissue resembling classical WAT and the deeper adipose tissue resembling BAT. Gene expression analyses corroborated these findings, indicating a shift from WAT to BAT from superficial to deeper tissues, as the expression of the WAT-associated *LEP* gene decreased and that of the BAT-associated *UCP1* gene increased from superficial to deeper levels. In agreement with our study, Cypess et al. also concluded that humans possess BAT depots with features of classical BAT. This notion was based on the fact that the deeper adipose tissue depots (the one with the highest *UCP1* expression) displayed a gene expression profile resembling that of classical BAT; including higher expression levels of the two marker genes *ZIC1* and *LHX8* as compared with the superficial WAT. However, the authors did not exclude the presence of some beige adipocytes in the neck region as the beige marker gene *TNFRSF9* showed a tendency to be enriched in the deeper tissue and clustered the closest to *UCP1* after the two classical brown adipocyte markers *ZIC1* and *LHX8*.

Jespersen et al. recently published a study in which they explored the nature of human BAT from the supraclavicular region.[30] They compared the expression of proposed murine marker genes for classical brown, beige and white adipocytes in supraclavicular BAT from patients undergoing surgery for suspected cancer in the neck area to that in subcutaneous abdominal WAT. As the tissue exhibited higher expression levels of the classical brown adipocyte markers *ZIC1*, *LHX8*, *miR-206*, and *miR-133b*,[29,31] and lower expression levels of *HOXC8* and *HOXC9*,[29] two genes preferentially expressed in beige and white adipose depots as compared with classical brown depots, the authors concluded that human supraclavicular BAT contains classical brown adipocytes. However, in agreement with the study by Wu et al., the authors also found that the proposed beige selective genes *TBX1* and *TMEM26* were preferentially expressed in the BAT as compared with the reference WAT. Hence, the authors suggested that human supraclavicular BAT might consist of both classical brown and beige adipocytes.

Taken together the three studies provide sound evidence for the notion that humans actually possess the two distinct kinds of brown adipocytes previously found in rodents. This is important since it argues for the possibility of extending our knowledge of BAT physiology in rodents to humans. At the same time the studies highlight some difficulties of studying human BAT in general and when

subtyping it as being classical brown or beige in particular.

First, the origin of the analyzed samples is a matter of concern. In the optimal situation the samples are taken from healthy subjects. However, as mentioned above, biopsies of neck BAT are often taken from patients with thyroid or parathyroid pathologies. It is well known that thyroid hormone, as well as thyroid-stimulating hormone, affect BAT and its activity,[32,33] and despite normal serum levels during sampling of BAT, potential effects on BAT phenotype cannot be excluded.

Second, it is important to stress that the cellular heterogeneity in the sampled tissue is a complicating factor when deciding if a certain BAT depot consists of classical brown or beige adipocytes. So far most studies have used the overall gene expression profile of an entire adipose depot for the classification. This is troublesome since BAT, especially depots assigned as being beige, represents a tissue containing both white and beige adipocytes. As indicated in the study by Jensen et al.,[30] a mix of white, beige, and classical brown adipocytes might coexist at least in the supraclavicular region further complicating the analyses.

A connected issue is how gene expression patterns should be compared. Most commonly the expression profile of the BAT depots under study has been compared with that of reference WAT samples collected either from the same subject or from another group of subjects. The reason for this is most likely that it is relatively easy to get access to subcutaneous WAT samples. However, the comparison to WAT might be a complicating factor since also different WAT depots display different gene expression patterns.[29] A way to avoid this problem would be to compare one BAT depot with another BAT depot, ideally from the same subject.

Even if several marker genes have been suggested to distinguish classical brown from beige adipocytes, these markers need to be further validated. As implied above, the cellular heterogeneity in BAT is a complicating issue, and studies dedicated at validating marker genes should attempt to use more homogenous brown adipocyte populations. Such homogeneity can be achieved either by establishing clonal cell lines from the different BAT depots, as did Wu et al.,[24] or by isolating classical brown or beige adipocytes from different BAT depots using microdissection techniques. Both approaches have their pros and cons. Clonal cell lines exhibit unmatched cell homogeneity, but the cells might have lost some of their original properties. Microdissection is an attractive alternative as it allows for the isolation of a relatively pure cell population directly from its original context. However, when comparing the gene expression patterns of cells isolated from different BAT depots by this technique, one should be open for the possibility that detected differences might reflect the fact that the cells have been isolated from spatially different locations rather than denoting actual differences in cellular identity. For example, *Zic1* appears to be the gene that best discriminates between iBAT and beige BAT in mice as its expression is readily detected in iBAT but is almost absent in beige BAT.[29] Therefore this gene appears to be a suitable marker gene for classical brown adipocytes vs. beige adipocytes, and its preferential expression in certain BAT depots of humans has been used as an indication of the existence of classical brown adipocytes in humans.[26,27,30] Caution should however be taken not to use the *ZIC1* expression alone as a proof of classical brown adipocyte identity as the gene encodes a transcription factor that has been suggested to be involved in dorsoventral body patterning presenting with a preferential expression in the dorsal module of vertebrates.[34,35] Although the expression of the gene persists in cells isolated from iBAT when grown in vitro,[36] it remains to be verified that *ZIC1* represents a true marker for classical brown adipocytes in humans and not just reflects the location from which such cells have been isolated.

Up to now most attempts to find marker genes that distinguish classical brown, beige, and white adipocytes have been done on cells or tissue derived from mice. Although likely, it remains to be confirmed that suggested markers apply also to humans. From the discussion above it is clear that new reliable marker genes for human classical brown and beige adipocytes would be of great value for the future studies of BAT. Most importantly both types of brown adipocyte express *UCP1*, a gene exclusively expressed in these cells that can quickly dissipate chemical energy stored as triglycerides as heat. The findings discussed here suggest that the development and the physiological regulation of BAT in rodents and humans are comparable. Although there might be significant differences, we can to a large extent build on the existing knowledge derived from animal models when trying to find ways to activate and/or expand BAT in humans in order to tackle obesity and associated diseases.

Disclosure of Potential Conflicts of Interest

S.E. is shareholder and consultant to Ember Therapeutics.

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