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**Human BAT possesses molecular signatures that resemble beige/brite cells.**

**Journal:** PLoS One

**Publication Year:** 2012

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**PubMed link:** 23166672

**Funding Grants:** Specialty in Stem Cell Biology

**Public Summary:**

Brown adipose tissue (BAT) is a thermogenic fat depot that generates heat and dissipates energy to protect animals from cold and obesity. Rodents possess two types of brown fat cells (adipocytes) that share a unique protein, but arise from different developmental lineages. One cell type is the "classical" brown adipocyte that is developed before birth. This cell type shares the same progenitors as muscle cells. Brown adipocytes from this lineage comprise the brown fat depot that is present at birth. The other cell type is known as "Beige" or "Brite". These cells arise in white adipose tissue depots in response to external stimuli such as cold or specific receptor agonists. Beige or Brite cells share the same lineage as white fat cells. Beige or Brite cells have inducible characteristics that make them a promising therapeutic target for obesity treatment; however, the relevance of this cell type in humans remains unknown. In this study, we determined the genes being expressed by the two types of brown adipocytes found in rodents; the beige cells after they were induced using a known stimulus, and the classical, pre-existing brown fat cells. We then observed which genes were being expressed in human BAT samples isolated from multiple adipose depots. When we compared the gene expression patterns in human BAT with those in the two rodent BAT cell types we found that nearly all the human samples showed a gene profile similar to that in Beige or Brite cells—and not with the classical, pre-existing brown fat. This suggests that human BAT may contain inducible types of cells that respond to changing needs for heat production. If these cells are truly beige/brite cells in humans, it could be possible to engineer more human BAT as a therapeutic measure for those suffering from obesity. The gene expression pattern we observed in human BAT was closely correlated with the expression of other genes that encode for molecules that direct precursor cells to become brown fat. This is important to help confirm that these human BAT depots are active by showing that their regulators and directors are also being actively produced in human tissues. Furthermore, using immunostaining we identified a new beige cell marker that is only expressed in beige cells in mice and in human BAT – but not in classical brown adipocytes in mice. All together, our findings suggest that human BAT appears more similar to rodent beige/brite cells than to the classical brown adipocytes found in rodents. As it is possible to induce the formation of new clusters of beige/brite cells in mice with the proper stimulus, it might also be possible to engineer or induce the formation of more active brown fat in humans. If the mechanism and regulation of the formation of human brown fat can be further investigated and delineated, and targeted in a way similar to that done in the murine counterpart, it could prove a useful and powerful tool in combating the obesity epidemic we face today.

**Scientific Abstract:**

Brown adipose tissue (BAT) dissipates chemical energy and generates heat to protect animals from cold and obesity. Rodents possess two types of UCP-1 positive brown adipocytes arising from distinct developmental lineages: "classical" brown adipocytes develop during the prenatal stage whereas "beige" or "brite" cells that reside in white adipose tissue (WAT) develop during the postnatal stage in response to chronic cold or PPARgamma agonists. Beige cells' inducible characteristics make them a promising therapeutic target for obesity treatment, however, the relevance of this cell type in humans remains unknown. In the present study, we determined the gene signatures that were unique to classical brown adipocytes and to beige cells induced by a specific PPARgamma agonist rosiglitazone in mice. Subsequently we applied the transcriptional data to humans and examined the molecular signatures of human BAT isolated from multiple adipose depots. To our surprise, nearly all the human BAT abundantly expressed beige cell-selective genes, but the expression of classical brown fat-selective genes were nearly undetectable. Interestingly, expression of known brown fat-selective genes such as PRDM16 was strongly correlated with that of the newly identified beige cell-selective genes, but not with that of classical brown fat-selective genes. Furthermore, histological analyses showed that a new beige cell marker, CITED1, was selectively expressed in the UCP1-positive beige cells as well as in human BAT. These data indicate that human BAT may be primarily composed of beige/brite cells.

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