OVERVIEW

Paracrine, endocrine and neurocrine controls of the adipocyte color phenotype: view from the chair

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After a long drought caused by misjudged irrelevance to human biology, the research field of brown adipose tissue has seen a period of resurgence since 2009 when discoveries of brown fat in adults were reported. However, the molecular and physiological regulators of the different types of adipose tissues—white, beige or brown—are still far from being fully determined. Speakers of the morning session of the 16th Annual Symposium of the Université Laval's Chair in Obesity, a series interestingly launched in 1998 precisely on the topic of uncoupling proteins, presented past and recent findings on non-adrenergic signaling pathways—both upstream and downstream—regulating the metabolic and thermogenic activities of adipose tissue. They went on to show that these pathways are altered in the contexts of obesity and aging, the latter being a very important factor involved in the decline of non-shivering thermogenesis. Whereas opinions diverged on readily applicable solutions for development of candidate therapeutics, the panelists agreed that the new factors involved in the control of the adipose thermogenic program hold great promise for innovation. This will likely depend on how this novel knowledge is integrated into the complex regulation of thermogenesis, which will be achieved through better-defined experimental protocols, both in humans and non-human models.

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Brown adipose tissue (BAT) is very fascinating. Research on this tissue has been the source of pioneering discoveries for a very ebullient 20-year period, some directly related to thermogenesis and UCP1, and others to the metabolic impact of altered BAT activity. For instance, the massive role of BAT in the uptake of energy fuels (especially free fatty acids) in periods of cold exposure has been highlighted since 1986, when it was shown that hypotriglyceridemia occurs despite higher hepatic triglyceride secretion, an effect in large part due to free fatty acid entry and oxidation in BAT.^{1–3} Subsequently, the field entered a 10-year period of 'hibernation' caused by a sadly increasing lack of interest based on the absence of evidence in adult humans. In a brilliant and astonishing manner, this gloomy era has then been rapidly overturned by the discovery of high metabolic activity and energy fuel turnover in symmetrical tissues, confirmed non-tumorous, which were then identified as BAT by thorough molecular analyses.^{4–9} This marked the beginning of a renewed phase of great interest in BAT research, which benefited both from technical advances (especially in cellular and molecular biology), and from a much increased workforce in the obesity research community that developed gradually after the discovery of leptin 15 years before. Whereas some established findings were then revisited and elegantly confirmed with better technical tools, for example, the contribution of BAT to cold-induced hypotriglyceridemia,¹⁰ important novel discoveries have now changed the way we understand the complex pathways involved in non-shivering thermogenesis, including the many types/colors of adipocytes. The morning session of the symposium was specifically focused on the dissemination of innovative developments regarding non-adrenergic modulators of beige and BAT.

Dr James G Granneman (Wayne State U, Detroit, MI, USA) fittingly started the session by offering a historical perspective from the early moments to the 'Renaissance' of BAT research. He

pointed to the work of Foster and Frydman¹¹ that showed BAT as the dominant site for noradrenaline-stimulated thermogenesis, and highlighted that of Rothwell and Stock¹² on diet-induced BAT thermogenesis as a major trigger for interest in the field. Still, Dr Granneman observed that it remains difficult today to ascribe diet-induced changes in responsiveness of BAT to noradrenaline in a body weight-independent manner. This narrative led to a very lively discussion on β 3-adrenergic receptor agonists and the reasons for their failure in clinical trials, as well as a perspective on the therapeutic potential of novel BAT stimulators such as retinoic acid and TGR5 agonists. Participants deemed thyroid hormone mimetics or receptor modulators risky at this point, especially considering their cardiovascular impact, but rather turned their attention to novel important factors in the cellular fate of 'brown-in-white' (brite), or beige adipocytes. These cells might represent a massive source of recruitable thermogenic powerhouses, which could be useful to dissipate extra energy in the context of obesity, and, possibly more importantly from a therapeutic viewpoint, to serve as a sink for metabolic fuels in the context of diabetes.^{13,14}

The lineage tracing of brown and beige adipocytes differs. In rodents, whereas classical brown adipocytes, located in the interscapular depot, come from Myf5+ precursor cells, beige adipocytes are mostly located in subcutaneous fat (inguinal depot) and derive from Myf5– cells. This dichotomy was best illustrated by the discovery of the PRD1-BF1-RIZ1 homologous domain containing 16 (PRDM16)-induced myocyte (also Myf5+)-to-brown adipocyte switch, which was elegantly described during the presentation of Dr Shingo Kajimura (UCSF, San Francisco, CA, USA), who was directly involved in the history of this discovery. However, whether humans possess either brown or beige fat remains debated. This is important to study because the presence of only brown fat, being less extensible in mass than the beige depot, could limit the usefulness of thermogenic stimulators in the

clinic. Advances in whole-genome technologies will allow a better portrait compared with previous candidate gene approaches, and multiple, independent and unbiased experiments may reveal whether the 'genomic signatures' of human UCP1+ cells resemble those of rodent beige or brown adipocytes. Combined positron emission tomography with computed tomography imaging could also be used to look at novel depots showing metabolic activity upon cold exposure, which would suggest recruitable beige rather than brown fat.

The molecular control of beige and brown adipocytes is not yet fully known. Dr Kajimura offered us a presentation of his newly (within the same week) accepted paper on EHMT1, which works as a histone methyltransferase protein that is required for PRDM16 activity.¹⁵ This suggests that parental gene imprinting may influence the baseline repression of browning genes targeted by the EHMT1/PRDM16 complex. Identifying those genes and how their imprinting levels fluctuate with diet or other long-term metabolic disturbances could represent an attractive follow-up.

Dr Yu-Hua Tseng (Harvard Medical School, Boston, MA, USA) extended the discussion on the topic of non-adrenergic regulators of the thermogenic cellular program. After introducing brain-derived neurotrophic factor, irisin, heart-derived natriuretic peptides and FGF21 as powerful browning agents, she centered her presentation on bone morphogenetic proteins (BMPs) and on her own recently published (6 months before the symposium) article. Whereas several BMPs exist, Dr Tseng previously demonstrated that only a few are involved in brown adipogenesis.^{16,17} However, Dr Tseng presented intriguing evidence that blocking BMP signaling by targeted disruption of the type 1 BMP BMPRI1A receptor induces an almost complete absence of classical BAT, but a compensatory increase in beige fat, leading to resistance to diet-induced obesity.¹⁸ This actually represents a valid proof-of-concept that beige fat is not only an expansible depot, which had been described by other groups notably through the AdipoChaser mouse model,¹⁹ but also its recruitment might hold greater therapeutic potential than classical BAT, as it is sufficient on its own for energy dissipation in the face of excess caloric intake. Although the full contributing role of the adrenergic system in this model remains to be unveiled, it nevertheless points to BMP signaling as a modulator mostly of brown, rather than beige adipose tissue.

The increasingly frequent use of positron emission tomography with computed tomography scanning to quantify the metabolic activity of brown and beige depots in adult humans²⁰ has allowed the study, in large cohorts, of the risk factors associated with a decline in their activity. It is now established that the prevalence of beige depots is higher in people younger than 50 years of age compared with patients older than 64 years; in fact, studies have indicated that aging is a strong (if not the strongest) factor contributing to the decline of beige fat in humans.^{7,21–23} A study also showed that adolescents exhibit a higher prevalence (40%) compared with adults (5–10%).²⁴ This age-related decline in beige fat is thought to be the result of a gradual reduction in thermogenic activity of present adipocytes, as well as altered differentiation of new beige cells in rodents and humans.^{25–28} Dr Roy Smith (Scripps Florida Research Institute, Jupiter, FL, USA) described his recent findings on the age-associated transition from beige to white fat occurring in subcutaneous adipose tissue. Such loss of beige adipocytes upon aging is easily visible by classical histology,²⁷ and is associated with a reduced 'beige signature'—gene markers such as *Ucp1*, *Prdm16*, *cidea*, *cox7a1* and *PPARalpha*,²⁸ indicative of an important genomic reprogramming. What initiates such transition remains uncertain, although clear defects in *de novo* differentiation of beige cells are observed.²⁸ In addition, a diminution in tissue blood flow owing to a decrease in angiogenesis during life could contribute to a diminished thermogenic capacity. In contrast, as Dr Tseng mentioned, a reduction in autophagy favors brown adipogenesis.³¹ This is paradoxical, as increased autophagy is linked to prolonged life

span in several model organisms. The role of autophagy in age-induced loss of brown/beige adipose tissue may thus be complex. Perhaps, the most challenging topic is how to prevent the decline in beige fat function upon aging, which perhaps might have a profound impact on other age-associated metabolic disorders such as diabetes and cardiovascular diseases.

Overall, the findings presented during a cold November morning were exceptionally impressive, both by the quality and originality of the research. Although many intriguing questions remain, the novel pathways regulating the thermogenic potential of adipose tissue may provide very exciting opportunities. Research on beige/BAT is undoubtedly not going to go into a second hibernation any time soon.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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DISCLAIMER

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