Perspectives on the role of brown adipose tissue in human body temperature and metabolism

Camilla Scheele1,2,*

In this Backstory, Camilla Scheele shares the journey of her group’s research on human brown adipose tissue leading up to the study of winter swimmers’ thermoregulation and energy expenditure (https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00266-4) appearing in this issue of Cell Reports Medicine.

Do winter swimmers have more brown fat?
Brown adipose tissue (BAT) is an intriguing, healthy, and hopeful version of the otherwise not so popular fat. BAT is a fat tissue that instead of associating with disease, produces heat, increases energy expenditure, and correlates with traits for cardiometabolic health. This sparks the imagination, and one question I often get, after explaining that brown fat is activated by cold, is “what about winter swimmers—do they have more BAT?” Winter swimming has become extremely popular in Scandinavia, not the least during the recent year when COVID-19 forced people out of restaurants and nightclub to explore life in nature. The idea of investigating BAT activation in winter swimmers was therefore tempting to push forward. Cold-water immersion goes beyond simple exposure to a cold air environment, because body temperature decreases much faster. Meanwhile, winter swimmers kept contacting us about how invigorated they felt from the cold baths and again asking if we thought this was related to an increased amount of brown fat. Although we work on human tissues and cells, my lab at the Novo Nordisk Foundation Center for Basic Metabolic Research (CBMR) is more of a basic research lab. We study characteristics, development, and heterogeneity of human adipocytes, with a specific focus on human thermogenic adipocytes as a source of secreted metabolic regulators. It was therefore obvious that if we wanted to perform an in vivo study, this would require collaboration.

Seamless communication with clinical departments
I did my post-doc at the Centre for Physical Activity Research (CFAS). This translational center is located at Rigshospitalet, the main research hospital in Copenhagen. For multiple studies, CFAS has not only functioned as a portal to access precious clinical material from the hospital, but it is also a place where physicians, physiologists, and molecular biologists join forces to answer basic research questions or to perform preclinical studies. It was here that I was fortunate to get involved in the early characterization of human BAT, which was published in 2013. The story goes back in time to when my PhD supervisor arranged a research stay at the lab of the BAT legends, Barbara Cannon and Jan Nedergaard, at Stockholm University. In their lab, I learned how to isolate adipocyte progenitors from BAT of mice and how to differentiate them in vitro into functional brown adipocytes. When I later started my post-doc in Copenhagen, people considered me as someone with BAT experience and I got involved in an exciting project on human BAT. This was right before several studies came out with PET/CT scanning evidence that adult humans have active BAT. It took slightly longer for us, but we came in the second wave, adding to the controversial discussion on whether human BAT is brown or beige. With the markers available at that time, we found an overlap of beige and brown markers in human BAT compared to white adipose tissue. Today, we know that human BAT contains thermogenic adipocytes, whereas heterogeneity in terms of activity occurs at both the tissue and cellular level. Importantly, we have isolated adipocyte progenitors from the supraclavicular deep neck as well as perirenal adipose tissue, which can differentiate into thermogenic adipocytes in vitro. The protocol for isolating human adipocyte progenitors is derived and modified from what I learned during my period in Barbara Cannon’s and Jan Nedergaard’s lab before moving to Copenhagen. By collaborating with physicians who perform surgery in the neck region or who do kidney transplantations, we have accessed BAT from adult humans and

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have isolated adipocyte progenitors from around 100 individuals. When transferring to CBMR in 2016, I stayed in close contact with CFAS. In fact, my husband, Søren Nielsen, is a senior researcher there, working on non-coding RNA in adipocyte metabolism, so we keep up a daily and (almost) seamless communication.

**Connected by an underground tunnel system**
The gold standard method for measuring brown fat activity is PET/CT-scanning. This is not a trivial method and definitely not something easily established in any lab. However, the Department of Clinical Physiology, Nuclear Medicine and PET and the Cluster for Molecular Imaging at Rigshospitalet routinely performs PET scans for cancer diagnostics. Importantly, CBMR, CFAS, and the main building of Rigshospitalet are all located within walking distances. In fact, all three buildings are connected by an underground tunnel system (further explored in Lars von Trier’s brilliant TV series “Riget,” or in English, “The Kingdom”). Via CFAS, we thus established a collaboration with the Department of Clinical Physiology at Rigshospitalet. At this point, I recruited Susanna Søberg, a talented PhD student who turned out to be the perfect fit for this project, which demanded extreme organizational skills as well as practical medical experience and physiological insight. She optimized the cooling protocol based on previous studies and with great support from our clinical collaborators at the Department of Clinical Physiology, winter swimmers and control subjects could be scanned for brown fat activity during cooling or at thermal comfort. Coordinating the subjects with a team of physicians, engineers, and lab assistants, Susanna was able to pull the experimental part through, and then we only had to interpret and write up the data.

**Unexpected results and the missing piece of the puzzle**
We hypothesized that winter swimmers would have a higher induction of their BAT in response to cooling. This hypothesis built on multiple studies demonstrating an increased BAT activity following repeated cold treatment or pharmacological activation. However, this was not what we found in the young healthy winter swimmers. We were first intrigued to see that most of the control subjects had some BAT activity during thermal comfort, but we were even more intrigued that BAT was completely turned off in all winter swimmers, at least in terms of glucose uptake. One possible explanation was a modified regulation of glucose uptake in the winter swimmers, and maybe an increased uptake and usage of lipids. Talking against this idea was previous human studies showing that repeated cooling resulted in increased BAT glucose uptake. We sent the first submission of the paper with a discussion around this intriguing data but without any clear-cut explanation. The editorial decision came on Christmas Eve 2020. While sipping on an eggnog, I was relieved to learn that the reviewers were overall positive, and the editor wanted to give us a chance to revise the manuscript. The reviewers were not only positive; they also helped us find the missing piece of the puzzle: heat acclimation! As a part of the winter swimming culture, people alternate between dipping in cold water and warming up in hot sauna. Revisiting our data with the heat exposure of the sauna in mind, we saw the connection between an inactive BAT at thermal comfort state and a lower core temperature in the winter swimmers, clearly arguing for heat acclimation. Our data thus pointed at a lower temperature baseline than in the control subjects and further suggested increased heat loss, altogether explaining the higher energy expenditure in response to cooling.

**Hypothalamus as a metabolic meeting point**
Following cold stimulus, sympathetic activation from the hypothalamus activates BAT. The hypothalamus is a fascinating structure, no larger than a pea in size, yet responding to peripheral impressions by forwarding hormonal and neuronal signals for coordinated control of whole-body metabolism. A specialized set of neurons in the hypothalamus also regulate the sleep-awake cycle, known as circadian rhythm. BAT has previously been described as being regulated by the circadian clock in mice, where BAT activity is first “turned on” just before mice wake up and “turned off” prior to mice falling asleep. Serendipitously, my office is next to Zachary Gerhart-Hines, a scientist who played a key role in uncovering the circadian BAT regulation in mice and who is a co-author on this winter swimming study. Interestingly, BAT is also an important organ in small hibernating animals, where it is involved in waking up animals periodically by producing heat at cyclic occasions during hibernation. Considering the
circadian control of rodent BAT and its function during hibernation, we were excited to see a highly pronounced peak in supraclavicular skin temperature in the winter swimmers, which preceded when the participants woke up. Our findings support a conserved role for human BAT in the arousal from sleep. From a broader perspective, the relationship between BAT activity and sleeping patterns in humans would be another interesting area of research to explore, not the least considering the increasingly recognized role of sleep quality for metabolic health.

Winter is coming
Humans have evolved to handle natural circles of light, temperature, and access to food. We need periods of sleep between being awake. Our metabolism also benefits from having periods of starvation between meals and periods of physical activity between being inactive (or the other way around). Regular physical exercise promotes a healthier metabolism, but what about temperature? Is exposure to different temperatures also beneficial for our metabolism? Growing up in Scandinavia, I am used to cold winters and warm summers, although we do a lot to prevent ourselves from freezing in the winter or being too hot in the summer. Our current data brings me back to my dear late Swedish grandmother who used to say: “man ska svettas in sommaren och frysa in vintern,” which means that you should continue wearing a warm jacket in the spring, sweating to prepare for summer, and continue wearing light clothing in the autumn, freezing to prepare for winter. This is a commonly known Swedish saying and it fits perfectly with the observations in the literature that humans activate a larger amount of BAT after a period of living in a cold environment, for example, in winter compared to summer. A key question to find out now is whether “training” your body to handle different temperatures is not just practical for staying at a comfortable body temperature or for increasing energy expenditure. Perhaps the effectiveness in keeping an optimal body temperature also plays a more integrated part in the complex attempt for a healthy metabolism?

DECLARATIONS OF INTEREST
The author declares no competing interests.