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Editorial

Brown Fat Develops a *Brite* Future

Martin Klingenspor[a] Stephan Herzig[b] Alexander Pfeifer[c]

[a]Molecular Nutritional Medicine, Technische Universität München, EKFZ – Else Kröner-Fresenius Center for Nutritional Medicine & Z I E L – Research Center for Nutrition and Food Sciences, Freising, [b]Joint Research Division Molecular Metabolic Control, German Cancer Research Center DKFZ, Center for Molecular Biology, NAR, Heidelberg University, University Hospital Heidelberg, Heidelberg, [c]Institute of Pharmacology and Toxicology, University of Bonn, Biomedical Center, Bonn, Germany

Brown fat is back in the obesity field. Since significant amounts of metabolically active adipose tissues were detected in adult healthy subjects after cold exposure and in patients undergoing routine diagnostics in nuclear medicine, the interest in brown fat is picking up pace again. Regarding the publication record during the past 50 years, brown fat has already went through several ups and downs (fig. 1). In a brief retrospective we here highlight important milestones in the field and briefly summarize the most recent developments without underestimating previous contributions made by many others.

In brown fat and hibernation research the first description of brown fat in a marmot by Conrad Gesner is legacy: 'They have a lot of fat on their back, although the other parts of the body are lean. In truth it can be called neither fat nor flesh, but similar to the bovine mammary gland, it is something in between'. [1]. More than four centuries later the function of brown fat as a heater organ was first recognized [2] and later confirmed by others [3]. Since then 9,180 papers on brown fat have been published (fig. 1).

The molecular catalyst of nonshivering thermogenesis in brown fat, uncoupling protein 1 (UCP1), was initially discovered as a 32 kDa purine nucleotide-binding protein in brown fat mitochondria [4, 5]. The first observations on the role of purine nucleotides and fatty acids in the respiratory control of brown fat mitochondria were already made early on [6, 7]. A detailed anatomical description of classical brown fat depots at different life stages in humans fueled speculations about its possible implications for human energy balance [8].

Based on the number of published papers per year, research in this field boomed for the first time after the seminal report on the function of brown fat in diet-induced thermogenesis in rats [9]. This coincided with the first in vivo measurements of tissue metabolic

Molecular Nutritional Medicine, Technische Universität München
EKFZ – Else Kröner-Fresenius Center for Nutritional Medicine & Z I E L – Research Center for Nutrition and Food Sciences
Gregor-Mendel-Straße 2, 85354 Freising
mk@tum.de

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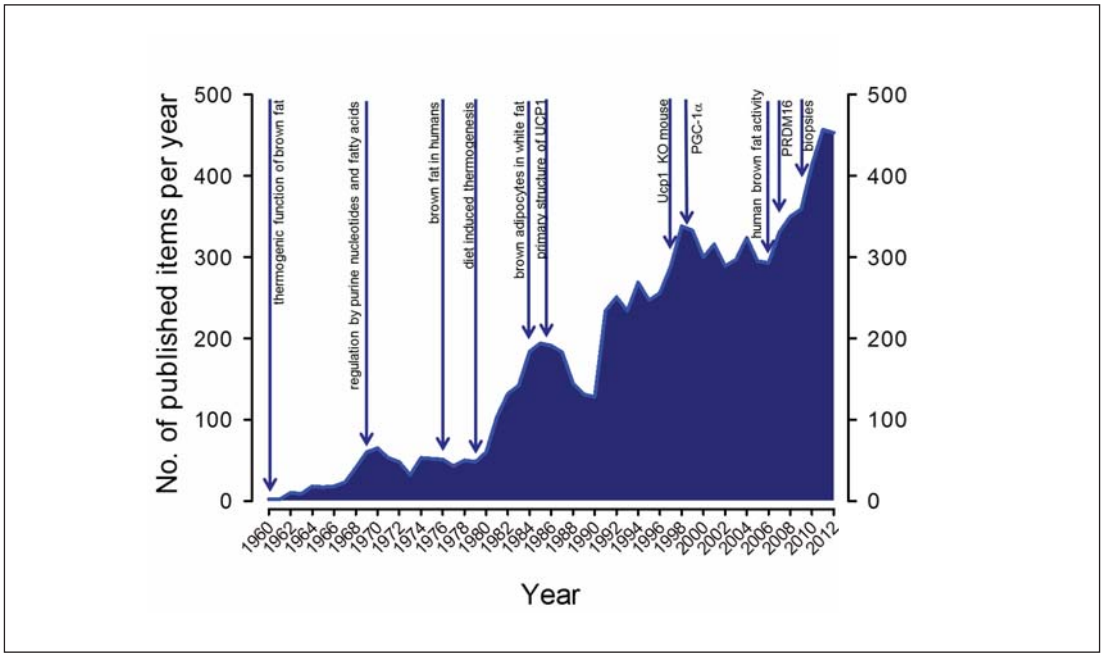

Fig. 1. Publication record of brown fat research from 1960 to 2012. The number of publications per year were searched in the Science Citation Index Expanded (Web of Science, Thomson Reuters) using the keyword string ('brown adipose tissue' OR 'brown fat' OR brown adipocyte*'). A total number of 9,180 publications were retrieved. Arrows indicate important progress in the field. PGC1-α = Peroxisome proliferator-activated receptor gamma coactivator 1 alpha; PRDM16 = PR domain zinc finger protein 16; UCP1 KO = uncoupling protein 1 knockout.

rates using radioactive microspheres in vivo, which confirmed the enormous heating capacity of brown fat [10]. An important discovery was that brown adipocytes are not restricted to classical brown fat depots but can also be found in typical white fat depots of mice. The abundance of these cells, nowadays termed brown-in-white (brite) or beige adipocytes [11, 12], is higher in cold-acclimated mice [13].

Subsequently, the primary structure of UCP1 was determined [14, 15] and a Ucp1 knockout mouse was generated which proved the essential function of brown fat in the defense against cold [16, 17]. Brown fat research also resulted in the identification of PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha), a master transcriptional regulator of mitochondrial biogenesis in mammals [18].

Despite this remarkable progress, the attention towards brown fat cooled off subsequently for several reasons. It was estimated that the small amounts of tissue in adult humans could not significantly contribute to total energy expenditure and thus would be negligible [19, 20]. Moreover, numerous attempts of pharmaceutical companies to develop potent agonists for beta-3-adrenergic receptors – the main receptor activated by sympathetic stimulation – to selectively recruit and activate brown fat in humans failed [21]. Thus, the translational potential of brown fat towards the development of novel strategies for obesity treatment was more or less neglected until 10 years ago, when hypermetabolic adipose tissue was observed by physicians in nuclear medicine by ^{18}fluor-deoxy-glucose positron emission tomography computerized tomography (FDG-PET-CT) and proposed to represent brown fat [22, 23]. In 2009 this proposal was confirmed independently by several groups [24–28]. Notably, these findings represent only one out of three novel highlights on

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brown fat biology which caught obesity and diabetes researchers by surprise and led to an impressive surge of publications.

Firstly, the ontogenetic origin of brown adipocytes was elucidated. Gene expression analysis had already indicated that brown and white adipocytes are derived from distinct precursor cell populations [29], with a muscle expression signature in brown fat preadipocytes [30]. Lineage tracing experiments in mouse models established that brown adipocytes in classical brown fat depots emerge from stem cells that express at some point during their ontogeny the muscle-specific gene *Myf5* (*myogenic factor 5*) [31–33]. This indicated that brown preadipocytes descend from the muscle lineage, and not from the adipose lineage of mesenchymal adipocyte progenitor cells. Indeed, the mitochondrial proteome of brown adipocytes and muscle cells reflect their common ontogenetic origin [34]. The transcriptional regulators PRDM16 (PR domain zinc finger protein 16) and C/EBPβ (CCAAT/enhancer-binding protein beta) play a major role in the cell fate decision process promoting the development of brown adipocytes from poorly characterized myoblast-like precursors [35].

Secondly, a significant amount of metabolically active brown fat is present in healthy adult humans. This was first revealed by modern imaging technologies FDG-PET-CT used in clinical tumor diagnostics to monitor tissue glucose uptake rate in vivo [36]. Radiologists observed unexpected large quantities of brown fat in the cervical, mediastinal, supraclavicular, paravertebral, and supra-/perirenal regions [28]. Experimental studies implementing repeated FDG-PET-CT scans on warm- and cold-exposed subjects uncovered a high prevalence of cold-activated brown fat in the majority of subjects under investigation [24, 25]. Retrospective analysis of clinical scans also demonstrated the presence of metabolically active brown fat in adults; however, these retrospective approaches appear to underestimate the prevalence of active brown fat [27, 37]. As glucose uptake is not a direct measure, other means to quantify thermogenic activity of brown fat in humans are currently applied. Along this line, the use of alternative PET-CT tracers has revealed increased metabolic rate and fatty acid oxidation in brown fat of cold-exposed human adults [38].

Thirdly, it has been demonstrated that the prevalence of brown fat in adult humans is negatively associated with the BMI, suggesting that reduced brown fat function may favor positive energy balance and facilitate the development of obesity [24, 25]. After maximal recruitment and activation, brown fat in rodents can dissipate heat with a power of nearly 500 W/kg when fully activated [39]. In humans, it had been estimated that even as little as 50 g of activated brown fat could account for up to 20% increased daily energy expenditure [9], and that up to 24% of the increase in metabolism in lean men produced by ephedrine can be attributed to brown fat activation [40]. More recent estimations based on the new FDG-PET data suggest that activated brown fat could burn 4 kg of body fat per year [28].

It is somewhat amazing that the presence of this metabolically active fat tissue in adults had been overlooked until recently. One explanation may be that visual inspection by naked eye rather reveals a ‘whitish’ appearance of adipose biopsies sampled from FDG-positive regions. Histological and molecular analysis of these biopsies demonstrates that they do not resemble the ‘pure’ brown fat phenotype normally found in newborns and rodents but rather represent white adipose tissue with interspersed thermogenically competent multilocular brite adipocytes. Transcriptome studies in human FDG-positive ‘brown fat’ identified high expression of several genes annotated in murine adipocytes as brite markers. This led to the conclusion that the FDG-positive adipose tissue in humans is not brown but rather brite fat [41, 42].

These findings raise the question what is the origin and physiological impact of brite adipocytes on energy metabolism? Since the first report on brite adipocytes [13], two concepts, namely transdifferentiation from white adipocytes and de novo recruitment of unknown adipocyte progenitor cells, have been put forward. Several findings support the

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presence of separate progenitor pools for white, brite and brown adipocytes. Adipocytes with a distinct expression signature that resembles brown fat cells have been characterized in primary cultures of the murine epididymal white fat depot [11], the different propensity of inbred mouse strains towards browning of white fat is maintained ex vivo in primary cultures [43], and clonal cell lines from stromal vascular fractions with distinct differentiation potential for white, brite and brown adipogenesis have been isolated [41]. However, the rapid appearance of brite adipocytes in white adipose tissue of cold-exposed rodents without an associated increase in adipocyte number rather supports the concept of transdifferentiation [44]. A synthesis of both concepts implicates that brite adipocytes may be equipped to express a much more metabolically flexible phenotype distinct from white and brown adipocytes. At rest these cells are in 'camouflage' adapting a white adipocyte-like phenotype but when activated by sympathetic neurons [45] or other paracrine [46, 47] or endocrine [48–51] signals rapidly express a brown adipocyte-like phenotype. Indeed, lineage tracing studies using constitutive and inducible reporter systems defined inducible brown adipocyte progenitors as Sca-1 (surface cell antigen 1), CD34 (hematopoietic progenitor cell antigen CD34) and PDGFRα (platelet-derived growth factor receptor alpha) positive [52], in contrast to white progenitors that express PDGFRβ and endothelial markers [53]. Interestingly, PDGFRα-positive progenitors developed into brown adipocytes under β3-adrenergic stimulation. In contrast, these cells differentiated into white adipocytes under conditions of high-fat diet feeding in vivo, demonstrating a bidirectional potential of brite cells depending on external stimuli [54]. Despite this progress, the exact nature of brown, brite, and white adipocyte progenitors still remains unsolved. There is strong support for the heterogeneity and regional specificity of these progenitors. In anterior fat depots of the body, in vivo lineage tracing has demonstrated that not only brown, as suggested previously [35], but also white adipocytes can emerge from Myf5-positive progenitors [55]. Moreover, not all adipocytes in mammals are of mesodermal origin, as adipocytes from the head region may originate from neuroectodermal progenitors [56].

So what is the metabolic function of brite fat in humans? Can metabolically active brite fat impact on the systemic metabolism of energy substrates, as implied by high rate of glucose uptake in cold exposed subjects? While brown and brite adipocytes do not seem to display increased cellular insulin sensitivity per se (K. Mössenböck and S. Herzig, unpublished observations), both basal and insulin-stimulated glucose uptake are substantially elevated as compared with white adipocytes. Thus, any white to brite fat transformation will increase the systemic glucose clearance and potentially also improve glucose tolerance and insulin sensitivity. Indeed, a number of clinical studies have validated substantial cold-induced glucose uptake in human subjects as measured by PET studies using FDG. Depending on the experimental setting, cold-stimulated glucose clearance through brite fat was enhanced between 4- and 15-fold, negatively correlating with BMI [24, 28].

Furthermore, insulin resistance is correlated with inflammation in white fat, and studies on the differential metabolic impact of distinct white fat depots and their capacities to recruit brown fat suggest that white to brite transformation could reduce inflammation and improve insulin resistance [57]. Finally, brown fat activity controls triglyceride and/or fatty acid clearance, thereby counteracting hypertriglyceridemia. In pathophysiological settings, cold exposure-corrected hyperlipidemia and improved deleterious effects of insulin resistance, which could be attributed to enhanced brown fat activation [58]. In addition, tracer studies in humans also underlined the potential of brite fat to efficiently take up fatty acids and use these substrates in oxidative metabolism [38, 59].

Finally, the enormous capacity of brite and brown adipocytes to dissipate energy and the recent scientific progress – especially the identification of active brite fat in human adults – underline the impact of this specialized fat tissue for energy balance and metabolism.

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The recent breakthroughs in the understanding of brown and brite fat ontogeny is promising and strongly suggests that we should seek for treatments to selectively promote the development and maintenance of brown and brite adipocytes. Future challenges lie in the exploration of the function and regulation of brown and brite adipocytes in both animal models and human subjects. Disturbances of normal physiological functions of brown and brite adipocytes may result in pathophysiological consequences and disease. In this light, it seems that the surge in publications on this hot topic will continue.

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