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EDITORIAL

Nutritional and metabolic regulation of brown and beige adipose tissues

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The last decade has witnessed an enormous interest of scientists and clinicians in the understanding of the biological activity of brown adipose tissue (BAT) and its role in health and disease. The importance of BAT as a relevant site of adaptive energy expenditure and protective properties against obesity and other metabolic alterations were growingly recognized in experimental animals after the seminal studies by Rothwell and Stock [22] and others in the late 1970s of the last century. However, the "re-discovery" of active BAT in adult humans in the last decade [11] has stimulated an unprecedented interest in BAT research.

BAT is a thermogenic tissue which main function is energy dissipation. Brown adipocyte thermogenesis is driven through uncoupling protein 1 (UCP1)-dependent and possibly also through UCP1-independent mechanisms (i.e., creatine-dependent substrate cycling, calcium-dependent ATP hydrolysis, lipid cycling) [8, 14].

BAT activity is inversely related to body fatness, and experimental suppression or activation of BAT leads to increased or decreased adiposity, respectively, indicating that BAT activation is protective against obesity. BAT activation is also involved in other metabolic roles, including control of glucose homeostasis and insulin sensitivity, as well as triglyceride clearance [1, 6, 7, 13]. BAT has also emerged as an active secretory organ that produces brown adipokines or "batokines," which may play an autocrine/paracrine role regulating the thermogenic function of brown adipocytes or other BAT cells (immune cells) or act as endocrine signals controlling the function of many other tissues including the liver, muscle, and white adipose tissue (WAT), among others [2, 4, 24] .

In addition to the so-called "classical" brown adipocytes, beige or brite (from "brown-in-white") adipocytes have been identified as a distinct type of adipose cells in rodents and humans sharing thermogenic properties with brown adipocytes [26]. The beige/brite adipocytes appear in WAT depots in a highly inducible manner through the process called adipose tissue "browning." The molecular characterization of BAT in adult humans has suggested that it may be composed of both classical brown adipocytes and beige/brite adipocytes [17, 23]. Although the relevant contribution of beige fat in the regulation of energy balance is controversial, a growing body of evidence suggests that stimulating the recruitment and activity of classical brown and beige adipocytes constitutes a promising strategy against obesity and its deleterious associated-disorders [18].

The abundance of brown/beige fat is reduced with obesity and aging. One of the current challenges is to unravel the mechanisms promoting the reduction of BAT/beige activity during aging, especially in humans, and to look for effective strategies to prevent BAT loss or to reactivate existing BAT depots [10].

The classically recognized mechanisms of control of BAT and beige adipose tissue rely on the sympathetic nervous

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Key points
- *Brown/beige adipose tissue regulates thermogenesis, glucose homeostasis, and triglyceride clearance.*
- *Brown/beige adipocytes function is regulated by central (hypothalamus) and peripheral signals (myokines, cardiokines, adipokines).*
- *Activation of brown/beige fat by nutrients and bioactive food components may constitute a strategy against obesity-related disorders.*

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system, which mediate cold and diet-induced thermogenic stimulus. However, in the last years, novel inducers of BAT activity and WAT browning have been identified, including metabolic, hormonal, and nutritional factors. The hypothalamus plays a key role orchestrating the central signals controlling BAT/beige fat activation [9]. Moreover, a dynamic cross-talk involving signals originating in key metabolic organs including the liver (fibroblast growth factor-21, FGF21), muscle (irisin, myostatin), heart (natriuretic peptides), or even the gut microbiota seems to play a relevant role in the control of brown/beige fat activation [5, 16, 25]. Changes in the levels of intracellular metabolites such as lactate and succinate are also involved in the regulation of adipose tissue thermogenesis [3, 19]. miRNAs have also been reported to regulate adipose tissue browning [12]. Besides pharmacological agents, the identification of nutritional factors and bioactive food compounds capable to induce BAT/beige activation, including omega-3 polyunsaturated fatty acids (n-3 PUFAs), polyphenols, capsinoids, or vitamin A-related compounds, is also attracting much attention [15, 20, 21]. The recognition of nutritional or pharmacological signals other than the sympathetic signaling capable to control BAT activity is especially important for strategies aimed to use BAT activity with therapeutic purposes, given the strong limitations due to side effects in the therapeutic use of sympathomimetics.

This special issue was designed to provide the reader with a comprehensive overview of emerging information on the metabolic, endocrine, and nutritional regulators of brown and beige adipose tissue activity. The issue collects original and review articles featuring the last knowledge about the role of the hypothalamic networks as well as of signals from muscle and adipocytes (autophagy and adipokines) in the regulation of BAT/beige activity. Moreover, the actions of specific metabolites (lactate) and bioactive food components (fatty acids and resveratrol) on BAT/beige activation are also extensively reviewed.

The interesting article of Efremova et al. found a higher percentage of brown-like adipocytes, expressing UCP1 in the mediastinal and perirenal fat (collected at necropsy), of human adults that lived in Siberia, especially in those living mainly outdoor. This fact was positively correlated with the adrenergic parenchymal innervation, suggesting that visceral fat can be converted to brown-like adipose tissue in adult humans under chronic cold exposure physiological conditions.

Contreras et al. review the latest knowledge about the mechanisms involved in the central regulation of BAT thermogenesis. The manuscript describes the role of different hypothalamic nuclei (preoptic and lateral area, as well as dorsomedial, paraventricular, ventromedial, and arcuate nucleus) in the control of BAT activity and WAT browning. The review focused in describing the molecular pathways involved and their implication in the development of obesity, based mainly in studies carried out in transgenic rodent models with targeted ablation or overexpression of key genes in specific neurons, as well as the possible human application of knowledge obtained from these rodent studies.

Cairó and Villarroya describe the role of autophagy in the intracellular processes that take place during brown/beige adipogenesis as well as on the regulation of thermogenesis. Autophagy seems to be inversely correlated to thermogenesis, contributing to the "whitening" (reversal of the browning) of adipose tissue and inactivation of thermogenic brown/beige adipocytes. Particularly, mitophagy through the regulation of the PINK1/Parkin system seems to play a key role for maintaining the mitochondrial pool when thermogenesis is active and removing the excess of mitochondria when thermogenesis is inactivated. Moreover, autophagic dysregulation in adipose tissues has been associated with obesity and its related metabolic diseases.

Physical exercise appears to stimulate the browning of WAT and, perhaps, BAT activity. Rodriguez et al. review the mechanisms by which physical exercise can do so, and how skeletal muscle established a cross-talk based on the release of myokines such as irisin, β-aminoisobutyric acid (BAIBA), follistatin, meteorin-like, decorin, and interleukin-6. Moreover, the ability of different adipokines (leptin, adiponectin, FGF21, zinc-α2-glycoprotein) to induce fat browning, as well as the potential cross-talk between WAT and skeletal muscle to control thermogenesis and body weight, is also discussed.

Metabolites are also emerging molecules involved in the control of brown/beige adipose tissues, and Carrière at al. extensively describe the emerging roles of lactate as a redox substrate and signaling molecule in adipose tissues. In their review, authors provide an overview of the recent findings showing that lactate acts as a sensing and signaling metabolite promoting brown and beige adipocyte development and activation. They also discuss other physiological roles of lactate including the dissipation of high redox pressure and oxidative stress through UCP1, contributing to redox homeostasis. All of these findings support that circulating metabolites such as lactate could be critical mediators of inter-organ cross-talk and important metabolic players of whole body energetic homeostasis.

In the context of the existing information on the biological role and functions of n-3 PUFAs, Fernández-Galilea et al. discuss the available preclinical (in vitro and in vivo) studies analyzing their thermogenic properties. Current evidences demonstrate that n-3 PUFAs, especially eicosapentaenoic acid (EPA), are regulators of the thermogenic program in brown/beige adipocytes, acting through UCP1-dependent and UCP1-independent (futile cycles) mechanisms. Some of these mechanisms involve the activation of the fatty acid receptor GPR120, the FGF21 production, the AMPK-SIRT1-PGC1-α signaling pathway activation, and the inhibition of

PGF_2 production. These preclinical studies have also suggested that supplementation of maternal diet with n-3 PUFAs might have anti-obesity effects in the offspring via epigenetic modifications.

Milton-Laskíbar et al. have reviewed the actions of resveratrol, a phenolic compound found naturally in grapes, berries, and peanuts, and its derivative pterostilbene, on BAT thermogenic activation and on WAT browning process. The current data in adipocytes cultures and animal models reveal that both resveratrol and pterostilbene promote thermogenesis in BAT and WAT browning. The manuscript focused in describing the molecular mechanisms involved as well as their effects on metabolic programming when administered during pregnancy or lactation. As occurs with the n-3 PUFAs, there is almost no evidence yet about the ability of resveratrol/pterostilbene to induce browning and thermogenesis in humans.

Overall, the studies collected in this issue evidence the biological diversity of the molecules and mechanisms that control BAT activity and WAT browning and, therefore, their capacity to modulate energy expenditure, glucose homeostasis, and lipidemia. As often occurring in biological research, strong advancements in experimental models are more limited in their application to humans, which indicate the importance to enhance translational research in this field to human patients. However, the advances reported here hold promise to the future development of pharmacological and/or nutritional-based strategies to take advantage of the extraordinary plasticity of adipose tissue to attain brown and beige phenotypes and therefore to promote metabolic health.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Bartelt A, Bruns OT, Reimer R, Hohenberg H, Ittrich H, Peldschus K, Kaul MG, Tromsdorf UI, Weller H, Waurisch C, Eychmüller A, Gordts PL, Rinninger F, Bruegelmann K, Freund B, Nielsen P, Merkel M, Heeren J (2011) Brown adipose tissue activity controls triglyceride clearance. Nat Med 17(2):200–205. https://doi.org/10.1038/nm.2297
2. Campderrós L, Moure R, Cairó M, Gavaldà-Navarro A, Quesada-López T, Cereijo R, Giralt M, Villarroya J, Villarroya F (2019) Brown adipocytes secrete GDF15 in response to thermogenic activation. Obesity 27(10):1606–1616. https://doi.org/10.1002/oby.22584
3. Carrière A, Jeanson Y, Berger-Müller S, André M, Chenouard V, Arnaud E, Barreau C, Walther R, Galinier A, Wdziekonski B, Villageois P, Louche K, Collas P, Moro C, Dani C, Villarroya F, Casteilla L Browning of white adipose cells by intermediate metabolites: an adaptive mechanism to alleviate redox pressure. Diabetes 63(10):3253–3265. https://doi.org/10.2337/db13-1885
4. Cereijo R, Gavaldà-Navarro A, Cairó M, Quesada-López T, Villarroya J, Morón-Ros S, Sánchez-Infantes D, Peyrou M, Iglesias R, Mampel T, Turatsinze JV, Eizirik DL, Giralt M, Villarroya F (2018) CXCL14, a brown adipokine that mediates brown-fat-to-macrophage communication in thermogenic adaptation. Cell Metab 28(5):750–763.e6. https://doi.org/10.1016/j.cmet.2018.07.015
5. Cereijo R, Giralt M, Villarroya F (2015) Thermogenic brown and beige/brite adipogenesis in humans. Ann Med 47(2):169–177. https://doi.org/10.3109/07853890.2014.952328
6. Chondronikola M, Volpi E, Børsheim E, Porter C, Annamalai P, Enerbäck S, Lidell ME, Saraf MK, Labbe SM, Hurren NM, Yfanti C, Chao T, Andersen CR, Cesani F, Hawkins H, Sidossis LS (2014) Brown adipose tissue improves whole-body glucose homeostasis and insulin sensitivity in humans. Diabetes 63(12):4089–4099. https://doi.org/10.2337/db14-0746
7. Chondronikola M, Volpi E, Børsheim E, Porter C, Saraf MK, Annamalai P, Yfanti C, Chao T, Wong D, Shinoda K, Labbè SM, Hurren NM, Cesani F, Kajimura S, Sidossis LS (2016) Brown adipose tissue activation is linked to distinct systemic effects on lipid metabolism in humans. Cell Metab 23(6):1200–1206. https://doi.org/10.1016/j.cmet.2016.04.029
8. Chouchani ET, Kazak L, Spiegelman BM (2019) New advances in adaptive thermogenesis: UCP1 and beyond. Cell Metab 29(1):27–37. https://doi.org/10.1016/j.cmet.2018.11.002
9. Contreras C, Nogueiras R, Diéguez C, Medina-Gómez G, López M (2016) Hypothalamus and thermogenesis: heating the BAT, browning the WAT. Mol Cell Endocrinol 438:107–115. https://doi.org/10.1016/j.mce.2016.08.002
10. Darcy J, Tseng YH (2019) ComBATing aging-does increased brown adipose tissue activity confer longevity? Geroscience 41(3):285–296. https://doi.org/10.1007/s11357-019-00076-0
11. Enerbäck S (2010) Human brown adipose tissue. Cell Metab 11(4):248–252. https://doi.org/10.1016/j.cmet.2010.03.008
12. Goody D, Pfeifer A (2019) MicroRNAs in brown and beige fat. Biochim Biophys Acta Mol Cell Biol Lipids 1864(1):29–36. https://doi.org/10.1016/j.bbalip.2018.05.003
13. Kajimura S, Spiegelman BM, Seale P (2015) Brown and beige fat: physiological roles beyond heat generation. Cell Metab 22(4):546–559. https://doi.org/10.1016/j.cmet.2015.09.007
14. Kazak L, Chouchani ET, Jedrychowski MP, Erickson BK, Shinoda K, Cohen P, Vetrivelan R, Lu GZ, Laznik-Bogoslavski D, Hasenfuss SC, Kajimura S, Gygi SP, Spiegelman BM (2015) A creatine-driven substrate cycle enhances energy expenditure and thermogenesis in beige fat. Cell 163(3):643–655. https://doi.org/10.1016/j.cell.2015.09.035
15. Laiglesia LM, Lorente-Cebrián S, Prieto-Hontoria PL, Fernández-Galilea M, Ribeiro SM, Sáinz N, Martínez JA, Moreno-Aliaga MJ (2016) Eicosapentaenoic acid promotes mitochondrial biogenesis and beige-like features in subcutaneous adipocytes from overweight subjects. J Nutr Biochem 37:76–82. https://doi.org/10.1016/j.jnutbio.2016.07.019
16. Li B, Li L, Li M, Lam SM, Wang G, Wu Y, Zhang H, Niu C, Zhang X, Liu X, Hambly C, Jin W, Shui G, Speakman JR (2019) Microbiota depletion impairs thermogenesis of brown adipose tissue and browning of white adipose tissue. Cell Rep 26(10):2720–2737.e5. https://doi.org/10.1016/j.celrep.2019.02.015
17. Lidell ME, Betz MJ, Dahlqvist Leinhard O, Heglind M, Elander L, Slawik M, Mussack T, Nilsson D, Romu T, Nuutila P, Virtanen KA, Beuschlein F, Persson A, Borga M, Enerbäck S (2013)

Evidence for two types of brown adipose tissue in humans. Nat Med 19(5):631–634. https://doi.org/10.1038/nm.3017
18. Loh RKC, Kingwell BA, Carey AL (2017) Human brown adipose tissue as a target for obesity management; beyond cold-induced thermogenesis. Obes Rev 18(11):1227–1242. https://doi.org/10.1111/obr.12584
19. Mills EL, Pierce KA, Jedrychowski MP, Garrity R, Winther S, Vidoni S, Yoneshiro T, Spinelli JB, Lu GZ, Kazak L, Banks AS, Haigis MC, Kajimura S, Murphy MP, Gygi SP, Clish CB, Chouchani ET (2018) Accumulation of succinate controls activation of adipose tissue thermogenesis. Nature 560(7716):102–106. https://doi.org/10.1038/s41586-018-0353-2
20. Montanari T, Pošćić N, Colitti M (2017) Factors involved in white-to-brown adipose tissue conversion and in thermogenesis: a review. Obes Rev 18(5):495–513. https://doi.org/10.1111/obr.12520
21. Okla M, Kim J, Koehler K, Chung S (2017) Dietary factors promoting brown and beige fat development and thermogenesis. Adv Nutr 8(3):473–483. https://doi.org/10.3945/an.116.014332
22. Rothwell NJ, Stock MJ (1979) A role for brown adipose tissue in diet-induced thermogenesis. Nature 281(5726):31–35
23. Shinoda K, Luijten IH, Hasegawa Y, Hong H, Sonne SB, Kim M, Xue R, Chondronikola M, Cypess AM, Tseng YH, Nedergaard J, Sidossis LS, Kajimura S (2015) Genetic and functional characterization of clonally derived adult human brown adipocytes. Nat Med 21(4):389–394. https://doi.org/10.1038/nm.3819
24. Villarroya F, Cereijo R, Villarroya J, Giralt M (2017) Brown adipose tissue as a secretory organ. Nat Rev Endocrinol 13(1):26–35. https://doi.org/10.1038/nrendo.2016.136
25. Villarroya F, Vidal-Puig A (2013) Beyond the sympathetic tone: the new brown fat activators. Cell Metab 17(5):638–643. https://doi.org/10.1016/j.cmet.2013.02.020
26. Wu J, Boström P, Sparks LM, Ye L, Choi JH, Giang AH, Khandekar M, Virtanen KA, Nuutila P, Schaart G, Huang K, Tu H, van Marken Lichtenbelt WD, Hoeks J, Enerbäck S, Schrauwen P (2012) Spiegelman BM. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. Cell 150(2):366–376. https://doi.org/10.1016/j.cell.2012.05.016