

Brown adipose tissue and the take (12,13-di)HOME message to the heart

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Obesity leads to insulin resistance, type 2 diabetes mellitus and it is a well-established cardiovascular risk factor.¹ Adipose tissue (AT) is a “biochemical factory” in the human body, and it plays a crucial role in human metabolism, while it secretes a wide range of bioactive adipokines/adipocytokines, with endocrine and paracrine effects on the cardiovascular system.² However, the location of the AT in the human body is a major determinant of its biological characteristics, with evidence suggesting that visceral adipose tissue is the one that drives cardiovascular disease, while subcutaneous AT has a rather “neutral” cardiovascular effect, and gluteal is even considered to exert cardio-protective effects.² In addition, AT biology is largely determined not only by its quantity but also by its quality and function.² To add to the complexity of AT biology, this tissue can be classified as white or brown AT (WAT or BAT) depending on its metabolic, morphological and broader biological phenotype. In humans WAT is the most abundant type and, besides being responsible for energy storage in the form of triglycerides, it has been proven to play a crucial role in regulating cardiovascular function.² WAT can indeed secrete bioactive molecules that affect cardiovascular biology and the diseased cardiovascular system can signal back to AT modifying its biology and function; this cross-talk plays an important role in cardiovascular disease development.²⁻⁶ On the contrary, BAT, which accounts for only 4.3% of the total fat mass in adults, is located in the interscapular, supraclavicular, mediastinal, paraspinal, and suprarenal area, and it is involved in energy expenditure, as it is the main site of non-shivering thermogenesis. Recent evidence suggests that BAT has a characteristic secretory profile as it releases “batokines” that contribute to its protective role against obesity and associated metabolic alterations, such as insulin resistance.⁷ It is also able to consume glucose and lipids for thermogenesis.⁷ Although increased BAT activity is believed to play a rather protective role against cardiovascular disease, there has been very little evidence for meaningful endocrine effects of BAT on either the heart or the vascular wall.^{8,9}

In this issue of *Circulation*, Pinckard and colleagues unravel the beneficial effects of BAT on cardiac function and they demonstrate the cardioprotective effects of the BAT-secreted lipokine 12,13-dihydroxy-9Z-octadecenoic acid (12,13-diHOME).¹⁰ This oxidized linoleic acid derivative is released from BAT in response to cold temperatures and exercise,^{11, 12} and previous work from the same group suggested that 12,13-diHOME regulates the BAT fuel uptake supporting its thermogenic function.^{11, 12} This also increases fatty acid uptake and mitochondrial fatty acid oxidation in skeletal muscle and it is inversely correlated with body-mass index (BMI) and insulin resistance.^{11, 12}

Despite the established role of 12,13-diHOME on BAT biology, its potential paracrine/endocrine effects on the heart have been unclear.¹³ Pinckard et al.¹⁰ observed that 12,13-diHOME plasma levels are lower in patients with heart disease.¹⁰ To understand the biological role of this lipokine, they used a mouse model to demonstrate that 12,13-diHOME counteracts the adverse effects of high-fat diet on cardiac function and remodelling in mice. 12,13-diHOME treatment also improved cardiac hemodynamics by acting directly on cardiomyocytes mitochondrial respiration through a mechanism that involves NOS1.¹⁰ This is a very important study as it shows that BAT can exert endocrine effects on the heart, and identifies 12,13-diHOME as a potential mediator of these effects. This first discovery calls for further research to better understand the nature of the cross-talk between BAT and the cardiovascular system in humans. Indeed, a thorough analysis of BAT secretome should be carried out in order to find other putative mediators of the endocrine protective role of BAT on cardiac function and remodelling; it would be interesting to explore the presence of a potential bi-directional communication between BAT and the cardiovascular system, similar to what has been demonstrated in the past for WAT.²⁻⁵

There is also evidence suggesting that 12,13-diHOME exerts similar effects on mitochondrial respiration of both skeletal muscle and cardiomyocytes;^{10, 12} it is therefore essential to now

understand whether this lipokine can affect mitochondrial function in vascular smooth muscle cells, as that would demonstrate its possible vaso-protective potential.

Concerning the translational implications, the authors observed an improvement in functional cardiac parameters after BAT transplantation in mice. BAT was believed to exist only in rodents and human neonates; however, in 2009 multiple retrospective studies using data collected from 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/computer tomography (CT) identified functional BAT in adult humans and this opened the way to consider it as a potential therapeutic tool to treat the metabolic dysregulation observed in obesity; recent preclinical studies have indeed shown that BAT transplantation successfully improves glucose metabolism, increases insulin sensitivity and decreases adiposity.¹⁴ The clinical relevance of this animal model has even augmented after demonstrating that human beige and brown adipocytes transplanted into mice improve glucose metabolism and reduce adiposity similarly to whole BAT transplantation.¹⁴ Beige or brite (brown-in-white) AT can be found interspersed in WAT depots, while WAT browning could be considered a promising alternative therapeutic approach; however, discrepancies between rodents and humans in WAT browning modulation² make this approach rather challenging.

Could targeting the bioavailability of 12,13-diHOME (e.g. by modulating its biosynthesis or its degradation) be a rational therapeutic approach to prevent the cardiovascular complications of obesity? More clinical studies are needed to clarify the upstream and downstream pathways involved in this lipokine synthesis and metabolism. Similarly, imaging of BAT could potentially reveal new imaging biomarkers with prognostic value in human cardiometabolic diseases. However, contrary to the rather easy assessment of WAT metabolic and inflammatory status using standard CT or PET/CT,¹⁵ BAT imaging is challenging given that it is hard to locate non-invasively, and its volume often falls below the detection limits of standard imaging tests such as PET/CT.

Overall, the concept of BAT as an endocrine organ is relatively new in humans; hence, the study of Pinckard and colleagues¹⁰ provides the first evidence implying that BAT can exert endocrine effects on the heart. Given the protective role of BAT in cardiometabolic health, the article by Pinckard et al.¹⁰ lays the foundations for establishing BAT and its “batokines” as therapeutic targets and/or diagnostic tools for cardiovascular diseases.

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CONFLICT OF INTEREST DISCLOSURES

Prof Antoniadis is a founder and shareholder of Caristo Diagnostics, a CT image analysis spinout company of the University of Oxford. Dr Badi has no conflicts to declare.

112 REFERENCES

- 113 1. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD,
114 Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA Guideline on the Primary Prevention of
115 Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association
116 Task Force on Clinical Practice Guidelines. *Circulation*. 2019; 140:e596-e646. doi:
117 10.1161/CIR.0000000000000678.
- 118 2. Oikonomou EK and Antoniades C. The role of adipose tissue in cardiovascular health and
119 disease. *Nat Rev Cardiol*. 2019; 16:83-99. doi: 10.1038/s41569-018-0097-6.
- 120 3. Margaritis M, Antonopoulos AS, Digby J, Lee R, Reilly S, Coutinho P, Shirodaria C, Sayeed R,
121 Petrou M, De Silva R, et al. Interactions between vascular wall and perivascular adipose tissue reveal
122 novel roles for adiponectin in the regulation of endothelial nitric oxide synthase function in human
123 vessels. *Circulation*. 2013; 127:2209-2221. doi: 10.1161/CIRCULATIONAHA.112.001133.
- 124 4. Gan L, Xie D, Liu J, Bond Lau W, Christopher TA, Lopez B, Zhang L, Gao E, Koch W, Ma XL, et
125 al. Small Extracellular Microvesicles Mediated Pathological Communications Between Dysfunctional
126 Adipocytes and Cardiomyocytes as a Novel Mechanism Exacerbating Ischemia/Reperfusion Injury in
127 Diabetic Mice. *Circulation*. 2020; 141:968-983. doi: 10.1161/CIRCULATIONAHA.119.042640.
- 128 5. Ogawa H, Ohashi K, Ito M, Shibata R, Kanemura N, Yuasa D, Kambara T, Matsuo K, Hayakawa
129 S, Hiramatsu-Ito M, et al. Adipolin/CTRP12 protects against pathological vascular remodelling
130 through suppression of smooth muscle cell growth and macrophage inflammatory response.
131 *Cardiovasc Res*. 2020; 116:237-249. doi: 10.1093/cvr/cvz074.
- 132 6. Tang X, Miao Y, Luo Y, Sriram K, Qi Z, Lin FM, Gu Y, Lai CH, Hsu CY, Peterson KL, et al.
133 Suppression of Endothelial AGO1 Promotes Adipose Tissue Browning and Improves Metabolic
134 Dysfunction. *Circulation*. 2020; 142:365-379. doi: 10.1161/CIRCULATIONAHA.119.041231.
- 135 7. Villarroja F, Cereijo R, Villarroja J and Giral M. Brown adipose tissue as a secretory organ.
136 *Nat Rev Endocrinol*. 2017;13:26-35. doi: 10.1038/nrendo.2016.136.
- 137 8. Raiko J, Orava J, Savisto N and Virtanen KA. High Brown Fat Activity Correlates With
138 Cardiovascular Risk Factor Levels Cross-Sectionally and Subclinical Atherosclerosis at 5-Year Follow-
139 Up. *Arterioscler Thromb Vasc Biol*. 2020; 40:1289-1295. doi: 10.1161/ATVBAHA.119.313806.
- 140 9. Zhou E, Hoeke G, Li Z, Eibergen AC, Schonk AW, Koehorst M, Boverhof R, Havinga R, Kuipers
141 F, Coskun T, et al. Colesevelam enhances the beneficial effects of brown fat activation on
142 hyperlipidaemia and atherosclerosis development. *Cardiovasc Res*. 2020; 116:1710-1720. doi:
143 10.1093/cvr/cvz253.
- 144 10. Pinckard K, Shettigar VK, Wright KR, Abay E, Baer LA, Vidal Souza P, Dewal RS, Das D, Duarte-
145 Sanmiguel D, Hernández-Saavedra D, et al. A novel endocrine role the BAT-released lipokine 12,13-
146 diHOME to mediate cardiac function. *Circulation*. 2020. doi: 10.1161/CIRCULATIONAHA.120.049813.
- 147 11. Lynes MD, Leiria LO, Lundh M, Bartelt A, Shamsi F, Huang TL, Takahashi H, Hirshman MF,
148 Schlein C, Lee A, et al. The cold-induced lipokine 12,13-diHOME promotes fatty acid transport into
149 brown adipose tissue. *Nat Med*. 2017; 23:631-637. doi: 10.1038/nm.4297.
- 150 12. Stanford KI, Lynes MD, Takahashi H, Baer LA, Arts PJ, May FJ, Lehnig AC, Middelbeek RJW,
151 Richard JJ, So K, et al. 12,13-diHOME: An Exercise-Induced Lipokine that Increases Skeletal Muscle
152 Fatty Acid Uptake. *Cell Metab*. 2018; 27:1111-1120 e3. doi: 10.1016/j.cmet.2018.03.020.
- 153 13. Bannehr M, Lohr L, Gelep J, Haverkamp W, Schunck WH, Gollasch M and Wutzler A. Linoleic
154 Acid Metabolite DiHOME Decreases Post-ischemic Cardiac Recovery in Murine Hearts. *Cardiovasc*
155 *Toxicol*. 2019; 19:365-371. doi: 10.1007/s12012-019-09508-x.
- 156 14. White JD, Dewal RS and Stanford KI. The beneficial effects of brown adipose tissue
157 transplantation. *Mol Aspects Med*. 2019; 68:74-81. doi: 10.1016/j.mam.2019.06.004.
- 158 15. Antonopoulos AS, Sanna F, Sabharwal N, Thomas S, Oikonomou EK, Herdman L, Margaritis
159 M, Shirodaria C, Kampoli AM, Akoumianakis I, et al. Detecting human coronary inflammation by
160 imaging perivascular fat. *Sci Transl Med*. 2017; 9:eal2658. doi: 10.1126/scitranslmed.aal2658.