Vaibhav B. Patel[1,2] and Gavin Y. Oudit[1,2,3,4]

RESPONSE TO COMMENT ON PATEL ET AL.

ACE2 Deficiency Worsens Epicardial Adipose Tissue Inflammation and Cardiac Dysfunction in Response to Diet-Induced Obesity. Diabetes 2016;65:85–95

Diabetes 2016;65:e3–e4 | DOI: 10.2337/dbi15-0037

We appreciate the interest of Montaigne et al. (1) in our study on the regulatory role of angiotensin-converting enzyme 2 (ACE2) in obesity-associated epicardial adipose tissue (EAT) inflammation and its effect on cardiac structure and function (2). Recently, there has been a tremendous interest in studying the cross talk between EAT and the heart (3,4), and mice are a feasible model to study EAT effects on the heart. However, murine hearts possess a specific depot of EAT at the dorsal and dorsoventral sides of the atrioventricular grooves, unlike human hearts that are surrounded by very high amounts of EAT (5,6). The purpose of the gravimetric analysis in our study was to show a relative equivalent increase in the EAT levels in wild-type (WT) and ACE2 knockout high-fat–diet (HFD) groups. We are an experienced laboratory in murine cardiac surgeries, and the EATs from different groups were carefully collected under stereomicroscopy. We collected the EAT predominantly from the atrioventricular groove, and due to the low levels of EAT in mice, we pooled the EAT from three to four mice to perform our experimental assessment. It is also noteworthy that we used littermate WT control and ACE2 knockout mice at 6 months of age, in contrast to ~2 weeks to ~6 months of age in the studies cited by Montaigne et al. (6,7). In our study, littermate WT mice weighed ~40 g compared with ~32 g in the cited study (20% higher body weight compared with ref. 4 in the letter by Montaigne et al.) (7), and mice also received a 45% HFD (or a 10% control diet) for 23 weeks after weaning compared with 3 months of HFD in the study by Yamaguchi et al. (6). Böhm et al. (7) mentioned that only their HFD group showed detectable EAT; however, they did not report EAT weights, making it difficult to directly compare our results. Also, the gene expression analysis is reported as "fold increase" in mRNA expression in the EAT from the HFD group (possibly compared with the control groups).

In contrast to the comment by Montaigne et al. (1), Yamaguchi et al. (6) clearly showed the existence of EAT at the atrioventricular groove in mice as young as 2 weeks based on perilipin-positive adipocytes with progressive maturation of adipocytes with age. The authors performed various experiments to characterize the EAT in their murine models: histology showed that the EAT was subepicardial; retroaortic ink perfusion confirmed the coronary artery mediated perfusion of the EAT; and atrioventricular groove fat also showed the expression of brown adipose tissue–specific genes and pan-adipose genes, which is typically seen in human EAT. These three key findings led the authors to conclude that they were clearly able to identify, collect, and study the EAT (6). We concur that human tissues are the best candidate to assess the translational nature of the scientific findings. We also assessed the ACE2 levels and inflammatory status in the EAT obtained from nonfailing control and obese patients with heart failure with preserved ejection fraction, which essentially showed similar results to

[1]Division of Cardiology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada
[2]Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada
[3]Department of Physiology, University of Alberta, Edmonton, Alberta, Canada
[4]Alberta Diabetes Institute, University of Alberta, Edmonton, Alberta, Canada

Corresponding author: Gavin Y. Oudit, gavin.oudit@ualberta.ca.

our murine EAT and further validated our experimental findings (2).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Montaigne D, Coisne A, Marechal X, Staels B. Comment on Patel et al. ACE2 deficiency worsens epicardial adipose tissue inflammation and cardiac dysfunction in response to diet-induced obesity. Diabetes 2016;65:85–95 (Letter). Diabetes 2016;65:e1–e2. DOI: 10.2337/db15-1425

2. Patel VB, Mori J, McLean BA, et al. ACE2 deficiency worsens epicardial adipose tissue inflammation and cardiac dysfunction in response to diet-induced obesity. Diabetes 2016;65:85–95

3. Fontes-Carvalho R, Fontes-Oliveira M, Sampaio F, et al. Influence of epicardial and visceral fat on left ventricular diastolic and systolic functions in patients after myocardial infarction. Am J Cardiol 2014;114:1663–1669

4. Fitzgibbons TP, Czech MP. Epicardial and perivascular adipose tissues and their influence on cardiovascular disease: basic mechanisms and clinical associations. J Am Heart Assoc 2014;3:e000582

5. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. Nat Clin Pract Cardiovasc Med 2005;2:536–543

6. Yamaguchi Y, Cavallero S, Patterson M, et al. Adipogenesis and epicardial adipose tissue: a novel fate of the epicardium induced by mesenchymal transformation and PPARγ activation. Proc Natl Acad Sci U S A 2015;112:2070–2075

7. Böhm C, Benz V, Clemenz M, et al. Sexual dimorphism in obesity-mediated left ventricular hypertrophy. Am J Physiol Heart Circ Physiol 2013;305:H211–H218