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Perivascular Adipose Tissue and Inflammation

Adam G Goodwill

Department of Cellular & Integrative Physiology, Indiana University School of Medicine, Indianapolis IN

Keywords

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Dear Editor: The manuscript by Viera-Potter *et al*. entitled “Disconnect Between Adipose Tissue Inflammation and Cardiometabolic Dysfunction in Ossabaw Pigs” determined that high fat diet fed Ossabaw swine developed many of the hallmarks of obesity in the absence of marked adipose tissue inflammation(1). While the investigators should be lauded for an ambitious examination of a relevant model of obesity, there are methodological concerns that warrant discussion.

Initial investigation into adipose derived paracrine factors was performed by production of an adipose-conditioned media. These data are difficult to interpret based on: 1) the juvenile status of the animal and the parallels drawn to inflammatory status in adult animal models and humans 2) the unaddressed potential for experimentally induced influences on the adipose secretome. Perivascular adipose tissue (PVAT) has been demonstrated to exhibit a reduced state of differentiation(2). Therefore, 24-hours of culture could result in secretion of factors by tissues whose differentiation was determined by *ex vivo* conditions. Similar studies employing a non-targeted proteomic screen of secreted factors in media conditioned for 30 minutes have identified 186 differentially regulated proteins between adipose from lean and obese Ossabaw swine. Secreted factors from obese Ossabaw PVAT were demonstrated to exacerbate underlying endothelial dysfunction and dose-dependently increase tension development in isolated coronary arteries from either lean or obese Ossabaw regardless of the presence of a functional endothelium(2). Therefore, while the study by Vieria-Potter *et al*. provides quantitative, targeted measures of classically defined inflammatory cytokines, the culture conditions and absence of previously documented vasomotor actions should be further investigated.

As PVAT is a heterogenous cell population, the Padilla group utilized cell-sorting (FACS) to determine the populations of cells within adipose depots. A concern for these findings is the use of CD68 as a primary macrophage marker for the analyses. While CD68 has been shown to stain swine alveolar macrophages via immunohistochemistry, it failed to identify macrophages in any other porcine tissues. By contrast, staining in that same study was found

Please address correspondence to: Adam G. Goodwill, PhD, Indiana University School of Medicine, MS2067, 635 Barnhill Drive, Indianapolis, IN 46202.

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in numerous tissues from multiple species. Moreover, staining intensity was notably diminished in porcine alveoli relative to humans, the impact of which is impossible to assess in this study as the authors did not provide dot-plots for the FACS analyses(3). This calls to question the utility of CD68, a marker that has been shown to also have significant reactivity with endothelial cells, fibroblasts, and lymphocytes, as a macrophage marker for this study(4). Additionally, the authors highlight the anti-inflammatory nature of CD163 expressing macrophages. CD163 macrophages, which produce both pro- and anti-inflammatory cytokines, are known hemoglobin-haptoglobin scavengers and have been found at the site of microbleeds providing the alternative hypothesis that the presence of CD163 macrophages may have less to do with adipose derived signaling than with microbleeding at the site of the developing atherosclerotic plaque or leaky vaso-vasorum(5).

Although the work by Vieria-Potter *et al*. addresses the intriguing topic of adipose tissue inflammation in a juvenile model of cardiovascular disease, additional studies are required to address methodological issues which mitigate impact of the findings.

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