Published in final edited form as:

Clin Sci (Lond). 2016 November 01; 130(22): 2101–2104. doi:10.1042/CS20160628.

Adipose inflammation at the heart of vascular disease

Michael V. Autieri*

*Department of Physiology, Independence Blue Cross Cardiovascular Research Center, Lewis Katz School of Medicine at Temple University, Philadelphia, PA 19140, U.S.A.

Abstract

Visceral adipose tissue is a primary site of chronic inflammation in obesity and may contribute to systemic inflammation and development of atherosclerotic vascular disease. Few studies identify molecular mechanisms and secretory pathways which mediate this process. In this edition of *Clinical Science*, Kwok et al. utilize a transgenic mouse in which dominant-negative c-Jun NH2 terminal kinase (dnJNK) expression is restricted to adipose tissue to implicate JNK-driven expression of adipocyte fatty acid binding protein (A-FABP) in visceral adipose tissue as a key secretory pathway to exacerbate development of atherosclerosis in ApoE^{-/-} mice. They further demonstrate that ApoE^{-/-} mice transplanted with visceral adipose tissue in which JNK has been inactivated display less systemic inflammation and develop significantly less atherosclerosis compared with control mice. Together, the findings of the present study reinforce our understanding of visceral adipose tissue as a secretory organ and the importance of the JNK/A-FABP pathway in mediating adipose vascular cross-talk and exacerbation of atherosclerosis.

Keywords

atherosclerosis; inflammation; white adipose tissue

Despite dietary modification and lipid lowering medications, atherosclerotic vascular disease is a significant medical and socioeconomic problem and continues to account for 50% of all mortality in the United States. It will worsen with an increasing number of patients with co-morbidity such as obesity, metabolic syndrome and Type 2 diabetes mellitus; conditions linked with atherosclerotic vascular disease [1]. Clearly, characterization of molecules and a better understanding of pathways in which these co-morbidities contribute to development of atherosclerosis can lead to more efficacious therapeutics and reduced morbidity and mortality. Atherosclerosis is a chronic lipid-driven inflammatory disease involving multiple cell types which are activated by an exquisitely regulated interplay of pro- and anti-inflammatory cytokines. It has long been recognized that these cytokines are produced and recognized by numerous cell types, lymphocytes, macrophage, endothelial and vascular smooth muscle cells, among others which communicate with each other through a series of cytokine-receptor mediated interactions [2]. It is becoming increasingly appreciated that adipocytes and adipose tissue are also capable of synthesis of cytokines which may participate in the atherosclerotic process.

Obesity results from a prolonged imbalance between energy intake and energy expenditure, and is an independent risk factor for a number of chronic diseases, including cardiovascular disease and atherosclerosis [1]. Recent studies in both mice and humans demonstrate that low-grade chronic inflammation has emerged as a potential causative link between obesity and cardiovascular disease [3–5]. Visceral adipose tissue is a primary site of chronic inflammation in obesity and is characterized by infiltration of a variety of immune cells, including macrophages, T-lymphocytes and neutrophils, all of which are capable of synthesis of pro-inflammatory cytokines. Adipose tissue is now considered to be a major endocrine organ, releasing cytokines termed adipokines. Through paracrine and exocrine signaling pathways, adipose tissue can communicate with other organs, including the vasculature. Expansion of adipose tissue in obesity therefore can potentially alter synthesis and secretion of proinflammatory adipokines which may contribute to vascular inflammatory diseases. In this scenario, cross-talk between expanding pro-inflammatory adipose tissue can exacerbate the vascular response to inflammatory stimuli, such as excess oxidized LDL, promoting development of atherosclerosis. Indeed, Ohman et al. [6] showed that ApoE^{−/−} mice transplanted with visceral fat had increased levels of pro-inflammatory adipokines and developed significantly more atherosclerosis compared with mice transplanted with subcutaneous fat, which is somewhat resistant to inflammation. It has been suggested that characterization of the adipose secretome would identify biomarkers and soluble causative factors which would link obesity and cardiovascular disease [7]. What is needed is more complete identification of molecular mediators which link inflamed visceral tissue and the vasculature, and characterization of maladaptive cellular pathways activated by this pro-inflammatory cross-talk.

In this issue of *Clinical Science*, Kwok et al. [8] exploited a sophisticated and powerful animal model to specifically identify a molecular link between adipose inflammation and atherosclerosis. They extended their previous study in which they generated transgenic mice which expressed dominant-negative c-Jun NH2 terminal kinase (dnJNK) driven by the aP2 gene promoter in which dnJNK expression is restricted to adipose tissue [9]. The authors found that selective inactivation of c-Jun in adipose tissue protected mice from HFD-induced obesity and improved insulin sensitivity. Adipose-specific dnJNK mice also had an increase in energy expenditure and a decrease in systemic inflammation [9]. Why did the authors choose to investigate JNK as the molecular mediator linking adipose inflammation and atherosclerosis? It is well known that JNK activity is a central mediator of proinflammatory gene expression [10]. More apropos for the present study however, JNK is activated by inflammatory cytokines, and free fatty acids, both of which are elevated in hypercholesterolemia-driven development of atherosclerosis [11]. Indeed, the authors have previously found that JNK is activated in adipose tissue in obese mice, and that dnJNK protects against diet-induced obesity [9].

In the present study, Kwok et al. crossed the aforementioned adipose-specific dnJNK transgenic mice with ApoE^{−/−} mice to generate ApoE^{−/−}/dnJNK mice. In an initial experiment, they used this compound mouse to test the hypothesis that dnJNK/ApoE^{−/−} mice would be atheroprotected. Indeed, the authors observed reduced local adipose inflammation, indicated by significant reductions in macrophage infiltrate and JNK-targeted proinflammatory genes such as MCP-1, TNF α , Cox2 and adipocyte fatty acid binding

protein (A-FABP). Importantly, systemic inflammation, accumulation of visceral adipose tissue, and atherosclerotic lesion formation were all significantly reduced. This experiment confirms the importance of adipose tissue in development of atherosclerosis.

In mice as well as humans, the heart, small arteries and other blood vessels are surrounded by perivascular adipose depots, which like visceral adipose, may secrete adipokines [12]. Also similar to visceral adipose, perivascular adipose tissue expands and accumulates inflammatory cells in obese states. Therefore, it was possible that reduced atherosclerosis in dnJNK/ApoE^{-/-} mice may have been due to local effects, rather than secondary to a systemic reduction in inflammation. To eliminate this possibility, in a second experiment, epididymal adipose tissue isolated from obese dnJNK transgenic mice was transplanted into ApoE^{-/-} recipients, eliminating the possibility that JNK inactivation in perivascular adipose tissue participated in reduction in atherosclerosis. Mice receiving this graft demonstrated significantly reduced development of atherosclerosis, strongly suggesting that endocrine mediated adipose cytokine expression, rather than local, perivascular effects were capable of exacerbating atherosclerosis. Epididymal adipose transplantation also negates any effect of 'leakage' of the α 2 promoter, which may be activated in other cell types [13,14]. This experiment reinforces the concept that adipose tissue can act as an endocrine organ and contribute to atherogenesis.

Although adipose tissue is capable of secreting many proinflammatory cytokines, it was of obvious importance to define the major soluble effector synthesized by visceral adipose tissue that drives vascular inflammation. In the present study, A-FABP was the proinflammatory cytokine most effectively decreased by JNK inactivation, which is not surprising in that A-FABP is one of the most abundant proteins in mature adipocytes [15]. A-FABP acts as a lipid-binding chaperone for fatty acids [16] and also reduces eNOS activation, contributing to endothelial dysfunction [17]. Interest in A-FABP as a central mediator of obesity-related cardiovascular disease is supported by several studies suggesting that it potentiates lipid-induced inflammation [16]. In humans, plasma levels of this protein are higher than other adipokines, and A-FABP may be a biomarker for cardiovascular disease [18], suggesting a major role for A-FABP in adipose tissue endocrine communication. Correspondingly, when the authors infused recombinant A-FABP into dnJNK/ApoE^{-/-} mice, atherosclerosis development was comparable to control mice, suggesting that at least in the present study, A-FABP was a major soluble mediator of adipose-exacerbated atherosclerosis. This is not surprising for two reasons: first, macrophage-selective ablation of A-FABP has been shown to prevent the development of high cholesterol diet-induced atherosclerosis in ApoE^{-/-} mice [19,20]; and second, expression of A-FABP is dependent upon JNK transcriptional activation [21]. This experiment reinforces the notion that A-FABP is a major player in adipose-vascular cross-talk. A-FABP obviously does not act alone but in concert with other proinflammatory cytokines which undoubtedly participate in this process. An important future experiment would be to cross the dnJNK transgenic with an A-FABP^{-/-} mouse and transplant visceral adipose into ApoE^{-/-} mice to determine the necessity and potential of A-FABP to synergize with other proinflammatory adipokines. Equally important, JNK and A-FABP exhibit a reciprocal relationship in that JNK activity is necessary for A-FABP expression, and A-FABP potentiates JNK activity. Pharmacological inhibition or genetic deletion of one leads

to a decrease in the other, and A-FABP may amplify and sustain this feed-forward feedback loop [19]. Pre-clinical studies using A-FABP and c-Jun inhibitors show promise in reducing atherosclerosis in mouse models [22,23].

Ultimately, the present study by Kwok et al. [8] confirms and integrates disparate studies which implicate visceral adipose tissue as a secretory organ, and proinflammatory adipokines as important paracrine effectors of atherosclerosis. It points to the JNK/A-FABP axis as a high-value target to attenuate inflammation, and suggests future studies utilizing JNK inhibitors and A-FABP inhibitors to treat obesity-linked inflammatory diseases. In the big picture, it identifies candidate molecules which may clarify why obesity is a risk factor for atherosclerosis and why adipose tissue is at the ‘heart’ of vascular disease.

ACKNOWLEDGEMENT

We thank Matthew Autieri for original artwork on Figure 1.

FUNDING

This work was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health [grant numbers HL115575 and HL117724]; and the American Heart Association [grant number 13GRNT1685003 (to M.V.A.)].

Abbreviations:

A-FABP	adipocyte fatty acid binding protein
dnJNK	dominant-negative c-Jun NH2 terminal kinase

REFERENCES

1. Lenz M, Richter T and Muhlhauser I (2009) The morbidity and mortality associated with overweight and obesity in adulthood: a systematic review. *Dtsch. Arztebl. Int* 106, 641–648 PubMed [PubMed: 19890430]
2. Ross R (1999) Atherosclerosis—an inflammatory disease. *N. Engl. J. Med* 340, 115–126 CrossRef PubMed [PubMed: 9887164]
3. Hotamisligil GS (2006) Inflammation and metabolic disorders. *Nature* 444, 860–867 CrossRef PubMed [PubMed: 17167474]
4. Rosen ED and Spiegelman BM (2006) Adipocytes as regulators of energy balance and glucose homeostasis. *Nature* 444, 847–853 CrossRef PubMed [PubMed: 17167472]
5. Yudkin JS (2003) Adipose tissue, insulin action and vascular disease: inflammatory signals. *Int. J. Obes. Relat. Metab. Disord* 27, S25–S28 CrossRef PubMed [PubMed: 14704740]
6. Ohman MK, Shen Y, Obimba CI, Wright AP, Warnock M, Lawrence DA and Eitzman DT (2008) Visceral adipose tissue inflammation accelerates atherosclerosis in apolipoprotein E-deficient mice. *Circulation* 117, 798–805 CrossRef PubMed [PubMed: 18212290]
7. Lehr S, Hartwig S and Sell H (2012) Adipokines: a treasure trove for the discovery of biomarkers for metabolic disorders. *Proteomics Clin. Appl* 6, 91–101 CrossRef PubMed [PubMed: 22213627]
8. Kwok KHM, Bioch M, Cheng KKY, Hoo RLC, Ye D, Xu A and Lam KSL (2016) Adipose-specific inactivation of JNK alleviates atherosclerosis in ApoE-deficient mice. *Clin. Sci. (Lond.)* 130, 2087–2100 CrossRef PubMed [PubMed: 27512097]
9. Zhang X, Xu A, Chung SK, Cresser JH, Sweeney G, Wong RL, Lin A and Lam KS (2011) Selective inactivation of c-Jun NH2-terminal kinase in adipose tissue protects against diet-induced obesity and improves insulin sensitivity in both liver and skeletal muscle in mice. *Diabetes* 60, 486–495 CrossRef PubMed [PubMed: 21270260]

10. Ip YT and Davis RJ (1998) Signal transduction by the c-Jun N-terminal kinase (JNK)—from inflammation to development. *Curr. Opin. Cell Biol* 10, 205–219 CrossRef PubMed [PubMed: 9561845]
11. Hirosumi J, Tuncman G, Chang L, Görgün CZ, Uysal KT, Maeda K, Karin M and Hotamisligil GS (2002) A central role for JNK in obesity and insulin resistance. *Nature* 420, 333–336 CrossRef PubMed [PubMed: 12447443]
12. Eringa EC, Bakker W and van Hinsbergh VW (2012) Paracrine regulation of vascular tone, inflammation and insulin sensitivity by perivascular adipose tissue. *Vascul. Pharmacol* 56, 204–209 CrossRef PubMed [PubMed: 22366250]
13. Fu Y, Luo N, Lopes-Virella MF and Garvey WT (2002) The adipocyte lipid binding protein (ALBP/aP2) gene facilitates foam cell formation in human THP-1 macrophages. *Atherosclerosis* 165, 259–269 CrossRef PubMed [PubMed: 12417276]
14. Lee KY, Russell SJ, Ussar S, Boucher J, Vernochet C, Mori MA, Smyth G, Rourk M, Cederquist C, Rosen ED et al. (2013) Lessons on conditional gene targeting in mouse adipose tissue. *Diabetes* 62, 864–874 CrossRef PubMed [PubMed: 23321074]
15. Xu A and Vanhoutte PM. (2012) Adiponectin and adipocyte fatty acid binding protein in the pathogenesis of cardiovascular disease. *Am. J. Physiol. Heart. Circ. Physiol* 302, H1231–H1240 CrossRef PubMed [PubMed: 22210749]
16. Hoo RC, Yeung CY, Lam KS and Xu A (2008) Inflammatory biomarkers associated with obesity and insulin resistance: a focus on lipocalin-2 and adipocyte fatty acid-binding protein. *Expert Rev. Endocrinol. Metab* 3, 29–41 CrossRef
17. Lee MY, Li H, Xiao Y, Zhou Z, Xu A and Vanhoutte PM. (2011) Chronic administration of BMS309403 improves endothelial function in apolipoprotein E-deficient mice and in cultured human endothelial cells. *Br. J. Pharmacol* 162, 1564–1576 CrossRef PubMed [PubMed: 21175571]
18. Tso AW, Xu A, Sham PC, Wat NM, Wang Y, Fong CH, Cheung BM, Janus ED and Lam KS (2007) Serum adipocyte fatty acid binding protein as a new biomarker predicting the development of type 2 diabetes: a 10-year prospective study in a Chinese cohort. *Diabetes Care* 30, 2667–2672 CrossRef PubMed [PubMed: 17620449]
19. Makowski L, Boord JB, Maeda K, Babaev VR, Uysal KT, Morgan MA, Parker RA, Suttles J, Fazio S, Hotamisligil GS and Linton MF (2001) Lack of macrophage fatty-acid-binding protein aP2 protects mice deficient in apolipoprotein E against atherosclerosis. *Nat. Med* 7, 699–705 CrossRef PubMed [PubMed: 11385507]
20. Boord JB, Maeda K, Makowski L, Babaev VR, Fazio S, Linton MF and Hotamisligil GS (2002) Adipocyte fatty acid-binding protein, aP2, alters late atherosclerotic lesion formation in severe hypercholesterolemia. *Arterioscler. Thromb. Vasc. Biol* 22, 1686–1691 CrossRef PubMed [PubMed: 12377750]
21. Hui X, Li H, Zhou Z, Lam KS, Xiao Y, Wu D, Ding K, Wang Y, Vanhoutte PM and Xu A (2010) Adipocyte fatty acid-binding protein modulates inflammatory responses in macrophages through a positive feedback loop involving c-Jun NH2-terminal kinases and activator protein-1. *J. Biol. Chem* 285, 10273–10280 CrossRef PubMed [PubMed: 20145251]
22. Furuhashi M, Tuncman G, Görgün CZ, Makowski L, Atsumi G, Vaillancourt E, Kono K, Babaev VR, Fazio S, Linton MF et al. (2007) Treatment of diabetes and atherosclerosis by inhibiting fatty-acid-binding protein aP2. *Nature* 447, 959–965 CrossRef PubMed [PubMed: 17554340]
23. Wang J, An FS, Zhang W, Gong L, Wei SJ, Qin WD, Wang XP, Zhao YX, Zhang Y, Zhang C and Zhang MX (2011) Inhibition of c-Jun N-terminal kinase attenuates low shear stress-induced atherogenesis in apolipoprotein E-deficient mice. *Mol. Med* 17, 990–999 PubMed [PubMed: 21629969]

Figure 1. Relationship between obesity, JNK activation, adipokine production, systemic inflammation and vascular inflammation proposed by Kwok et al.

In obese individuals, JNK is activated, leading to activation of transcription factors and expression of numerous pro-inflammatory adipokines, including A-FABP which feeds forward and activates JNK to induce its own expression. A cocktail of multiple circulating pro-inflammatory adipokines, including A-FABP result in systemic inflammation. These pro-inflammatory adipokines lead to vascular inflammation, including atherosclerosis.