Journal of Molecular Biomarkers & Diagnosis

Ayari, J Mol Biomark Diagn 2015, 6:2
DOI: 10.4172/2155-9929.1000218

Mini Review Open Access

FABP4 Expression as Biomarker of Atheroma Development: A Mini-Review

Hanène Ayari*

University Lyon1, INSERM, ERI22, EA 4173, Lyon, France

***Corresponding author:** Hanène Ayari, EA4173, University Lyon1, Avenue Rockefeller, Lyon, France, Tel: 33684428699; Fax: 33477877515; E-mail: hananeayari@yahoo.fr

Rec date: Jan 08, 2015; **Acc date:** Jan 28, 2015; **Pub date:** Feb 02, 2015

Abstract

Atherosclerosis has been recognized as an inflammatory disease of the arterial wall. On the other hand, several studies in humans have linked Fatty acid binding protein 4 (FABP4) to coronary artery disease and its risk factors. In the literature, many experimental studies have provided strong evidence for the importance of FABP4 in the pathogenesis of cardiovascular disease. In a recent work, we proposed a potential role of FABP4 by inflammatory proteins in the generation of the atherosclerotic lesions. In conclusion, many results indicate that FABP4 is a key factor connecting vascular and cellular lipid accumulation to inflammation.

Keywords: Microarray; mRNA; Gene expression; FABP4; Inflammation; Atheroma plaque

Introduction

Atherosclerosis and its sequelae, including heart disease and stroke, are a major cause of morbidity and the leading cause of mortality in the world, and their incidence continues to rise worldwide [1-4]. Atherosclerosis has been recognized as an inflammatory disease of the arterial wall [5]. Endothelial activation by oxidized lipoproteins plays an important role in the initiation of the atherosclerotic lesion through increased adhesion of mononuclear cells and their recruitment into the vascular wall [5]. The recruited inflammatory cells induce the expression of inflammatory cytokines and chemokines, enhancing lesion progression. Accumulation of lipids and inflammatory cells and production changes in extracellular matrix by the vascular smooth muscle cells (VSMC) participate in the formation of advanced lesions. The inflammatory response also determines plaque composition and, as a result, strongly contributes to the occurrence of plaque complications that are responsible for clinically severe acute ischemic syndromes [2,6-9].

Association of FABP4 Enhanced Expression to Atherosclerosis

Several studies in humans have linked FABP4 to coronary artery disease and its complications [10]. Reduced FABP4 expression, as a result of a polymorphism in its promoter region, leads to a reduction in coronary artery disease events [11]. In addition, experimental studies have provided strong evidence for the importance of FABP4 in the pathogenesis of cardiovascular disease. Of particular interest is its capacity to mediate inflammatory effects [11,12].

The same study showed that FABP4 is important for several macrophage functions, including coordinating cholesterol trafficking, inflammatory activity and endoplasmic reticulum stress [11,13]. Fu S et al explain the importance of FABP4 during the development of atherosclerotic lesions, highlighting a central link between FABP4 expression and of macrophage stress development [13].

For our part, and in order to shed light on the role of FABP4 in atherosclerosis, mRNA gene expression was measured by an Affymetrix GeneChip Human Gene 1.0 ST arrays (Affymetrix, Santa Clara, CA, USA) using RNA prepared from 68 specimens of endarteriectomy from 34 patients. We studied by microarray analysis whether intact vascular tissue and carotid plaque from the same patient differ in FABP4 transcriptional profiling in response to atheroma formation. Gene microarray technology can be used to investigate global mRNA expression to identify mRNA populations that exhibit differential regulation in disease processes, thus providing important clues to the underlying molecular pathology.

Several efforts have been made to study large-scale gene expression in human atherosclerosis, for example by comparing gene expression in normal and atherosclerotic arteries. Changes involved in destabilization of the atherosclerotic plaque have been less in focus. The present study started from a large-scale microarray analysis in 34 patients to screen ADPF expression between MIT and arheroma plaque within the same individual. To our knowledge this is the first report comparing gene expression between MIT and atheroma carotid plaques. Our cohort of 34 patients included all consecutive patients admitted to university hospital of Lyon for carotid endarterectomy during 2009. Consequently, the microarray study has enough power to provide significant results at the genome-wide level.

In this study, we have used all available plaque tissue for mRNA quantification. An alternative would be to use only tissue from carefully characterized areas of plaque morphology. Similarly, we and several others have adopted microarray analysis to the whole plaque [14-16] but some groups have used only specific areas of plaque activity in their analysis [17-20]. Interestingly, despite the different approaches used, the results shared considerable similarity. This suggests that both approaches yield meaningful information and can be used to complement each other.

Besides, the Gene 1.0 ST Array uses a subset of probes from the Human Exon 1.0 ST Array and covers only well-annotated content. Each gene is represented on the array by approximately 26 probes spread across the full length of the gene, providing a more complete and more accurate picture of gene expression than 3' based expression

array designs; we deduce so that this would significantly strengthen our gene expression conclusions.

Concerning results interpretations, we have to keep in mind that atherosclerosis is a general disease and thus what we called 'intact tissue' is, in fact, already remodelled tissue. However, in human studies it is almost impossible to obtain real normal human tissue suited for gene expression analysis. Nevertheless, the intrapatient comparison allows us to draw conclusions about the atherogenic process per se.

We found that the enhanced expression of FABP4 correlates with an increase in CD36, CD68, CD52, CD163 and T-cell markers (unpublished results). Taken together, these results provide strong indications that FABP4 is a factor connecting vascular and cellular lipid accumulation to inflammation. This suggests that increased FABP4 expression in the atherosclerotic plaque is a risk factor for unstable carotid vascular disease with atherothrombotic complications. This augmented expression in the atheroma plaque could in part lead to more T-cells being activated, as reduced FABP4 has been shown to reduce T-cell proliferation and interferon-c production [21]. We also detected a correlation at the transcript level between FABP4 and adipophilin, which has been shown to participate in foam cell formation and increase at the levels of transcript and protein in symptomatic plaques [22]. We suggest a potential role of FABP4 by inflammatory proteins in the generation of the atherosclerotic lesions. The findings of the current study are consistent with those of Tsukamoto et al. and Hellings et al. who found that macrophage infiltration and lipid core size are major risk fatctors for developing atherosclerotic lesions [2,23-25].

In conclusion, our findings reveal a possible important role of FABP4 in coupling lipid accumulation inflammation and plaque formation. The mechanisms underlying this observation warrant further research, which will hopefully reveal new molecular targets for therapeutic applications stabilizing atherosclerotic plaques and preventing ischemic thromboembolic strokes.

Whereas, previous studies were performed in mouse models, so although a detailed molecular analysis was provided, this may not be analogous to the clinical setting. Our study therefore adds important data regarding the link between atherosclerotic patients and FABP4 expression, contributing to the complexity of inflammation and plaque instability. Overall, a more complete and comprehensive analysis is required. Further studies are needed to fully understand these mechanisms and the role of each specific FABP4 which will hopefully reveal new molecular targets for therapeutic applications against the development of atherosclerosis.

We will pursue our investigations vigorously until we find additional information and fully understand FABP4 role in atheroma development. For that purpose correlations between FABP4 mRNA levels and clinical status of the patients will be done. Adding these data may strengthen our data and will be the task for the future.

Acknowledgements

We specifically acknowledge Dr. H. OKBI for revision of the English.

References

1. Murray CJ, Lopez AD (1997) Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 349: 1269-1276.
2. Harjes U, Bridges E, McIntyre A, Fielding BA, Harris AL (2014) Fatty acid-binding protein 4, a point of convergence for angiogenic and metabolic signaling pathways in endothelial cells. J Biol Chem 289: 23168-23176.
3. Hung CS, Wu YW, Huang JY, Hsu PY, Chen MF (2014) Evaluation of circulating adipokines and abdominal obesity as predictors of significant myocardial ischemia using gated single-photon emission computed tomography. PLoS One 9: e97710.
4. Uehara H, Takahashi T, Oha M, Ogawa H, Izumi K (2014) Exogenous fatty acid binding protein 4 promotes human prostate cancer cell progression. Int J Cancer 135: 2558-2568.
5. Ross R (1999) Atherosclerosis: an inflammatory disease. N Engl J Med 340: 115-126.
6. Lee RT, Libby P (1997) The unstable atheroma. Arterioscler Thromb Vasc Biol 17: 1859-1867.
7. Parra S, Cabré A, Marimon F, Ferré R, Ribalta J, et al. (2014) Circulating FABP4 is a marker of metabolic and cardiovascular risk in SLE patients. Lupus 23: 245-254.
8. Fuseya T, Furuhashi M, Yuda S, Muranaka A, Kawamukai M, et al. (2014) Elevation of circulating fatty acid-binding protein 4 is independently associated with left ventricular diastolic dysfunction in a general population. Cardiovasc Diabetol 13: 126.
9. Yang Y, Thyagarajan N, Coady BM, Brown RJ (2014) Cholesterol efflux from THP-1 macrophages is impaired by the fatty acid component from lipoprotein hydrolysis by lipoprotein lipase. Biochem Biophys Res Commun 451: 632-636.
10. Yeung DC, Wang Y, Xu A, Cheung SC, Wat NM, et al. (2008) Epidermal fatty-acid-binding protein: a new circulating biomarker associated with cardio-metabolic risk factors and carotid atherosclerosis. Eur Heart J 29: 2156-2163.
11. Shi H, Wang Q, Wang Y, Leng L, Zhang Q, et al. (2010) Adipocyte fatty acid-binding protein: an important gene related to lipid metabolism in chicken adipocytes. Comp Biochem Physiol B Biochem Mol Biol 157: 357-363.
12. Saksi J, Ijäs P, Mäyränpää MI, Nuotio K, Isoviita PM, et al. (2014) Low-expression variant of fatty acid-binding protein 4 favors reduced manifestations of atherosclerotic disease and increased plaque stability. Circ Cardiovasc Genet 7: 588-598.
13. Fu S, Yang L, Li P, Hofmann O, Dicker L, et al. (2011) Aberrant lipid metabolism disrupts calcium homeostasis causing liver endoplasmic reticulum stress in obesity. Nature 473: 528-531.
14. Faber BC, Cleutjens KB, Niessen RL, Aarts PL, Boon W, et al. (2001) Identification of genes potentially involved in rupture of human atherosclerotic plaques. Circ Res 89: 547-554.
15. Randi AM, Biguzzi E, Falciani F, Merlini P, Blakemore S, et al. (2003) Identification of differentially expressed genes in coronary atherosclerotic plaques from patients with stable or unstable angina by cDNA array analysis. J Thromb Haemost 1: 829-835.
16. Adams LD, Geary RL, Li J, Rossini A, Schwartz SM (2006) Expression profiling identifies smooth muscle cell diversity within human intima and plaque fibrous cap: loss of RGS5 distinguishes the cap. Arterioscler Thromb Vasc Biol 26: 319-325.
17. Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, et al. (1995) A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Arterioscler Thromb Vasc Biol 15: 1512-1531.
18. World Medical Association Declaration of Helsinki (1997) Recommendations guiding physicians in biomedical research involving human subjects. Cardiovasc Res 35: 2-3.
19. Dhore CR, Cleutjens JP, Lutgens E, Cleutjens KB, Geusens PP, et al. (2001) Differential expression of bone matrix regulatory proteins in human atherosclerotic plaques. Arterioscler Thromb Vasc Biol 21: 1998-2003.

20. Papaspyridonos M, Smith A, Burnand KG, Taylor P, Padayachee S, et al. (2006) Novel candidate genes in unstable areas of human atherosclerotic plaques. Arterioscler Thromb Vasc Biol 26: 1837-1844.

21. Strengell M, Lehtonen A, Matikainen S, Julkunen I (2006) IL-21 enhances SOCS gene expression and inhibits LPS-induced cytokine production in human monocyte-derived dendritic cells. J Leukoc Biol 79: 1279-1285.

22. Schaer CA, Schoedon G, Imhof A, Kurrer MO, Schaer DJ (2006) Constitutive endocytosis of CD163 mediates hemoglobin-heme uptake and determines the noninflammatory and protective transcriptional response of macrophages to hemoglobin. Circ Res 99: 943-950.

23. Tsukamoto K, Kinoshita M, Kojima K, Mikuni Y, Kudo M, et al. (2002) Synergically increased expression of CD36, CLA-1 and CD68, but not of SR-A and LOX-1, with the progression to foam cells from macrophages. J Atheroscler Thromb 9: 57-64.

24. Hellings WE, Moll FL, De Vries JP, Ackerstaff RG, Seldenrijk KA, et al. (2008) Atherosclerotic plaque composition and occurrence of restenosis after carotid endarterectomy. JAMA 299: 547-554.

25. Hao Y, Ma X, Luo Y, Shen Y, Dou J, et al. (2014) Serum adipocyte fatty acid binding protein levels are positively associated with subclinical atherosclerosis in Chinese pre- and postmenopausal women with normal glucose tolerance. J Clin Endocrinol Metab 99: 4321-4327.