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Review Article

FABP4 EXPRESSION AS BIOMARKER OF ATHEROMA DEVELOPMENT: A MINI-REVIEW

Hanène AYARI

Université Lyon1, INSERM, ERI22, EA 4173, Avenue Rockefeller, Lyon, France.

Corresponding Author: hananeayari@yahoo.fr

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 morbidity and mortality in the world, and their incidence continues to rise worldwide (Murray CJ and Lopez AD, 1997). Atherosclerosis has been designed as an inflammatory disease of the arterial wall (Ross R, 1999). 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 (Ross R, 1999). The recruited inflammatory cells induce the expression of inflammatory cytokines and chemokines expression, enhancing lesion progression. Therefore, accumulation of lipids and inflammatory cells and production of 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 (Lee RT and Libby P, 1997).

Association of FABP4 enhanced expression to atherosclerosis

Several studies in humans have linked FABP4 to coronary artery disease and its complications (Yeung DC *et al*, 2008). Reduced FABP4 expression, as a result of a polymorphism in its promoter region, leads to a reduction in coronary artery disease events (Shi H *et al*, 2010). 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 (Shi H *et al*, 2010).

Other studies have shown that FABP4 is important for several macrophage functions, including coordinating cholesterol trafficking, inflammatory activity and endoplasmic reticulum stress (Shi H *et al*, 2010, Fu S *et al*, 2011). In line with this, the results of a recent study by 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 (Fu S *et al*, 2011).

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 endarterectomy 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.

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- γ production (Strengell M *et al*, 2006). 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 (Schaer CA *et al*, 2006). 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 K *et al* and Hellings WE *et al* who found that macrophage infiltration and lipid core size are major risk factors for developing atherosclerotic lesions (Tsukamoto K *et al*, 2002, Hellings WE *et al*, 2008).

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.

Previous studies was 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.

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Conflict interest: None

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