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

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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 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.

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 atheroma 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 factors 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.

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References


