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Mini Review

Adipophilin Expression in Atheroma Development: A Mini-Review

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Abstract

The expression of adipophilin [ADFP] seems to be elevated in atherosclerotic lesions compared with healthy arterial intima, it may play a role in the pathogenesis of atherosclerosis, notably in the transformation of macrophages into foam cells. It was proposed that adipophilin may play a key role in the lipid metabolism of foam cells and hence ultimately contributes to the formation of a lipid core in human atherosclerotic lesions. Several RNA microarray analysis showed that ADFP mRNA level was increased in carotid plaque compared with nearby intact tissue. For our part, we showed that atheroma plaque formation coincided with consequent adipophilin expression. Overall, a more complete and comprehensive analysis is required. Further studies are needed to fully understand these mechanisms and the role of each specific ADFP which will hopefully reveal new molecular targets for therapeutic applications against the development of atherosclerosis.

INTRODUCTION

The role of lipids is well established in the pathophysiology of atherosclerosis [1,2,3]. The permeability of dysfunctional atherosclerotic endothelium for blood lipoproteins increases, and blood-borne inflammatory cells accumulate within the arterial wall. The majority of lipoprotein particles captured into the vessel wall becomes modified, which leads to their uptake by macrophages and subsequent macrophage transformation into foam cells [4]. Adipophilin [ADFP], an adipose differentiation-related protein, is found in lipidcontaining cells [5], including macrophage foam cells. Its expression in macrophages is enhanced by modified LDL [6], and when expressed, it further enhances lipid accumulation and prevents lipid efflux from lipid-laden macrophages [7]. Because the expression of ADFP seems to be elevated in atherosclerotic lesions compared with healthy arterial intima, it may play a role in the pathogenesis of atherosclerosis, notably in the transformation of macrophages into foam cells [6].

ADFP has been studied previously in atherosclerotic lesions [5,7,8]. Accordingly, Larigauderie et *al* observed 3.5 times more intense ADFP expression in atherosclerotic lesions than in normal intima and found most of the ADFP mRNA expression of atherosclerotic lesions to be present within lipid-rich macrophages [6,7,8]. Besides, they suggested that ADFP expression is a consequence of cholesterylester retention within cells, and that ADFP further increases cholesterol accumulation by inhibiting its efflux from cells. It could be hypothesized that, by preventing lipid efflux from foam cells, ADFP contributes to their death and thereby participates in the growth of the confluent necrotic lipid core and the instability of the plaque. In addition, ADFP expression was strongly increased in plaques that had macroscopic ulceration, which lends further support to potential role of intraplaque hemorrhages. Wang *et al* also observed ADFP mRNA in macrophage-rich areas in atherosclerotic plaques, and they suggested that ADFP may play a key role in the lipid metabolism of foam cells and hence ultimately contributes to the formation of a lipid core in human atherosclerotic lesions [6].

For our part, and in order to shed light on the role of ADFP 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 ADFP transcriptional profiling in response to atheroma formation [unpublished results]. 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.

Microarray technology provides a rapid means to screen gene expression in the tissues of interest. Transcriptional profiling was based on Affymetrix Human GeneChip Gene 1.0 ST microarray [Affymetrix, Santa Clara, CA, USA] that is a whole transcript-based array for gene expression profiling. An important feature of the array is that, as for the Human Exon 1.0 ST array, it queries the entire transcript in contrast to most older Affymetrix arrays that query the 3' end of transcripts.

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 [9,10,11] but some groups have used only specific areas of plaque activity in their analysis [12,13,14,15]. 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*.

Using RNA microarray analysis, we examined the expression of this adipose differentiation-related protein in carotid atheroma. 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. The expression of ADFP mRNA was increased in carotid plaque compared with nearby intact tissue at mRNA level [2.27 fold, p=3.72E-07] [unpublished results]. Atheroma plaque formation coincided with consequent ADFP expression. Although further evidence is needed, our results support previous data. Importantly, some findings link ADFP to the hallmarks of complicated atherosclerotic plaques, *ie*, those with atherothrombosis, and thus well agree with the observation of overexpression of ADFP in the symptomatic carotid plaque phenotype.

To our knowledge, this is the first time that ADFP expression, at the mRNA level, has been studied using microarray approach in human arterial wall.

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 ADFP expression.

The idea is novel however we think that our data are preliminary. The limits of the study are that it is an isolated microarray study, without validation of the gene expression finding or any mechanism of action analysis to assess the relevance of the finding. The work requires as a minimum, RT-PCR and Western blot confirmation of the changes found in the microarray study. Inclusion of this data and histological immuno-histo-chemistry to show localization of the proteins within the lesions is required to prove our hypothesis. We will pursue our investigations vigorously until we find additional information and fully understand ADFP role in atheroma development. For that purpose correlations between ADFP 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.

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.

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