Lipid-Immunity Cross-Talk
A Role for Adipocyte Fatty Acid Binding Protein?

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Atherosclerotic disease remains a leading cause of death, despite significant improvements in treatment and prevention of primary disease manifestations. The increasing incidence of obesity and diabetes mellitus type 2 will further accelerate the global morbidity attributable to atherosclerotic disease. Atherosclerosis is considered an autoimmune-like inflammatory disease that proceeds in the presence of enhanced plasma cholesterol levels. Research groups that attempt to disentangle the pathogenesis of atherosclerotic disease often focus on either the role of the local inflammatory response or that of lipid metabolism and lipoprotein profiles. Answers to some unresolved questions in this research area could be obtained from studies that explore the cross-talk between lipids and inflammatory responses. There is sufficient evidence supporting the view that better understanding of the interaction between dyslipidemia and the immune response may help to unravel the pathogenesis of atherosclerotic disease progression. For example, it has been shown that lipid loading induces a distinct, unique gene expression profile in macrophages within the atherosclerotic lesion. In line with the induction of a specific gene expression profile upon lipid loading, monocytes from apolipoprotein E–deficient mice display marked changes in DNA methylation before atherosclerotic lesion formation. The humoral response also seems affected by lipid loading as effects of adjuvant on the immune response in apolipoprotein E–deficient mice differ from that of wild-type mice.

In the current issue of ATVB, a report is published from von Eynatten et al who studied plasma expression levels of a molecule that could function as a mediator at the interface of inflammation and lipid disorders in the context of atherosclerotic disease: adipocyte fatty acid binding protein (A-FABP, also abbreviated as FABP-4 or aP2). A-FABP is mainly expressed in adipocytes but also in plaque macrophages. A-FABP exerts multiple effects that influence the metabolic state such as regulating obesity induced insulin sensitivity. Furthermore, evidence is accumulating that A-FABP potentiates lipid-induced inflammatory responses. Excellent reviews have been published on the functionality of A-FABP, and a scheme is depicted in the Figure reflecting the functions of A-FABP that are relevant for cardiovascular disease development.

Both the biomarker and functional properties of A-FABP have been studied in relation to atherosclerotic disease. The expression of circulating A-FABP has been explored mainly in cross-sectional studies showing that levels were associated with different established risk markers of atherosclerotic disease such as obesity, high low-density lipoprotein levels, and endothelial dysfunction. In a follow-up study A-FABP was found to be predictive for development of diabetes mellitus type 2 or metabolic syndrome. In a plaque biobank study we showed that A-FABP strongly correlated with an unstable inflammatory plaque phenotype. Moreover, the plaque levels of A-FABP were strongly related with secondary manifestations of atherosclerotic disease during follow-up. In addition, genetic variability at the A-FABP locus results in decreased adipose tissue A-FABP expression. Individuals carrying the polymorphism in the A-FABP promoter revealed lower triglyceride levels, reduced risk for coronary artery disease, and diabetes mellitus type 2.

In line with the clinical findings, data from animal studies also support the pathogenetic role of A-FABP in cardiovascular disease. A-FABP deficiency resulted in a marked reduction of atherosclerotic lesions in apolipoprotein E–deficient mice. Inhibition of A-FABP using an antagonist resulted in a significant protection against atherosclerotic plaque formation in mice. Interestingly, the reported effects of A-FABP on atherosclerotic disease progression seem to be specific for macrophage-derived A-FABP.

Eynatten et al report that circulating A-FABP levels are associated with long-term prognosis in patients with coronary heart disease. This study included a 10-year follow-up with >200 major cardiovascular events. Although the predictive value of A-FABP for the occurrence of cardiovascular events was tested, the results will have more relevance from a pathogenesis perspective. The authors examined the strength of the marker by reclassification and found no incremental value of A-FABP above the traditional risk factors, which limits the potential value as a serological biomarker in prognostic research. The human follow-up study does, however, provide further support for the outcome of animal experiments showing that A-FABP is a pathophysiological mediator for atherosclerosis development.

The pharmaceutical community is striving for new suitable targets for intervention to halt progression of atherosclerosis. Before launching money- and time-consuming clinical trials, supportive evidence from human studies is urgently required to show that targeting the A-FABP holds promise. Human studies (genetic, plaque phenotype, and biomarker) as well as interventions in animals all reveal consistent results showing
that A-FABP functions at the interface of lipid metabolism and inflammatory responses and accelerates cardiovascular disease. Further investigations will provide the knowledge for the design of A-FABP antagonists to combat atherosclerotic disease. It is unknown whether A-FABP inhibitors can be safely used in humans. In addition, one could anticipate additional, yet unrecognized, pleiotrophic effects of drugs antagonizing adipocyte and circulating A-FABP. If successful, inhibition of A-FABP in humans may become a promising strategy to down tone the effects of metabolic diseases such as obesity and type 2 diabetes mellitus, on atherosclerosis disease progression.

### References


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