

NEWS AND COMMENTARY

# Lipoxygenases at the heart of atherosclerosis susceptibility

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It is well established that high levels of low-density lipoproteins (LDL) play a causal role in the etiology of atherosclerosis and the subsequent development of coronary artery disease (CAD) in man. Mainly through the work in cellular and animal models, a detailed molecular mechanism is emerging, which explains how pathogenic atherosclerotic lesions develop and can lead to myocardial infarction (MI) and stroke. In the prevailing model, LDL becomes oxidatively modified in the vessel wall, initiating the formation of an early fatty streak lesion consisting mainly of macrophages. Subsequently, a series of lipid-modifying enzymes have been identified in the vessel wall, capable of generating inflammatory mediators, which can further stimulate plaque growth by enhancing cellular influx.<sup>1</sup>

As long as 15 years ago, the presence of 12-lipoxygenase was demonstrated in human atherosclerotic plaques, and it was hypothesized that the activity of 12-lipoxygenase was crucial for the development of atherosclerotic disease.<sup>2</sup> Until recently, however, little evidence was obtained in human studies that supported this mechanism, and current therapies have remained focusing on lipid lowering as the principle therapeutic target. This situation is now likely to change very rapidly due to a series of breakthroughs in the field of human genetics that begin to close the gap between mouse models of disease and human disease.

How did this excitement take off? One of the lipid-modifying enzymes that have generated a lot of interest recently is 5-lipoxygenase (5LO). 5LO is produced by macrophages and is an important enzyme in the conversion of the lipid molecule arachidonic acid into leukotrienes. These leukotrienes are inflammatory mediators involved in monocyte attraction. Hence, 5LO may serve as a gene driving chronic inflammation and thereby the progression of atherosclerotic plaques. In line with this hypothesis, 5LO has recently been shown in genetic and knockout studies in mouse to play a major role in promoting plaque growth.<sup>3</sup> Based on these findings in mice, polymorphisms in the promoter of 5LO have been studied in patients and were correlated with the progression of lesion formation based on measurements of the thickness of the vessel wall.<sup>4</sup> These seminal observations place genes interacting with 5LO in a prime position as

candidate genes for CAD. Among those genes is ALOX5AP, encoding 5LO-activating protein (FLAP).

From a clinical point of view, however, an important question remains: can genetic mutations in this pathway affect crucial disease end points, such as MI and stroke? A recent study by Helgadóttir *et al*<sup>5</sup> from deCODE genetics elaborated successfully on this clinical question, by performing a linkage study in a large set of Icelandic families. Some 296 families were studied, including 713 patients with MI, generating a highly suggestive linkage peak to a locus on chromosome 13q. Subsequently, this chromosomal region was further investigated by association analysis with 120 microsatellite markers in a study including around 800 cases and controls. This screen resulted in the detection of a haplotype spanning two genes including ALOX5AP. Further studies using SNPs identified with certainty one particular ALOX5AP haplotype as the susceptibility gene in man for MI.

This role of ALOX5AP has also been demonstrated in an Icelandic cohort of patients with stroke and in CAD patients from the UK, although the UK patients differ in their risk haplotype. Hence, this genetic study now implicates a second gene of the lipoxygenase pathway in man to be the cause of cardiovascular disease, despite the fact that no *a priori* assumptions on candidate genes were made. This strong evidence for the role of the lipoxygenase pathways also renders the remaining genes of the pathway as attractive candidates to be studied genetically. Indeed, some of those genes, such as 12LO and phospholipases, have already been implicated in the progression of atherosclerotic lesions in rodent models.<sup>6,7</sup>

The study by Dwyer *et al*<sup>4</sup> has also addressed the crucial issue of gene–environment interactions by studying the effect of diet on 5LO promoter polymorphisms. First, a subgroup of carriers of a particular promoter variant was identified, which showed increased carotid artery intima-media thickness. Second, it was shown in these allele carriers that dietary arachidonic acid, the substrate for 5LO, increased the production of inflammatory mediators, as compared to subjects that were fed a ‘marine’ diet with N-3 fatty acids.

In addition to diets, drugs are available that can also modulate the lipoxygenase pathway. Particularly, the role of the 5LO pathway in disease is very well known in the

field of asthma research.<sup>8</sup> Therefore, a wide range of drugs that effectively block 5LO or leukotriene receptors is on the market. These drugs could now be of interest to prevent MI and stroke. It is very rewarding that these novel findings regarding the genetic susceptibility of CAD are perfectly in tune with the well worked out model for the etiology of atherosclerosis. The mechanism now established offers excellent opportunities to further study the possibilities for dietary prevention and pharmacological intervention.

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