Cysteinyl-Leukotrienes in Cerebrovascular Disease
Angels and Demons?

Magnus Bäck

Although the initial interest in the field of leukotriene (LT) research was focused on their potent bronchoconstrictive effects, subsequent studies have suggested LTs as key mediators in several inflammatory diseases. Genetic variations within the enzymes transforming arachidonic acid into LTs (Figure) have for example been associated with atherosclerosis and an increased risk of cardiovascular events.1

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Leukotriene C4 synthase (LTC4S; Figure) is a microsomal glutathione-S-transferase (mGST), which conjugates LTA4 with glutathione.2 The product, LTC4, shares its first enzymatic steps with glutathione to yield LTD4 and LTE4 (Figure). These 3 LTs, collectively referred to as the cysteinyl-LTs, exert their actions by means of at least 2 subclasses of CysLT receptors (Figure) expressed in airway and vessels, as well as on inflammatory cells.3 The CysLT1 receptor is the target for the clinically used antileukotrienes in asthma: montelukast, zafirlukast and pranlukast (Figure). The gene for LTC4S is mapped to the chromosome region 5q35, which is close to the cluster of cytokine genes associated with Th2 responses and asthma.2

In this issue of Arteriosclerosis, Thrombosis and Vascular Biology, Freiberg and coworkers have explored the association of ischemic stroke with polymorphisms in the proximity of the LTC4S gene.4 A single nucleotide polymorphism (SNP) in the LTC4S promoter was initially discovered in aspirin-intolerant asthmatics (AIA), a patient group particularly sensitive to the LTC4-induced bronchoconstriction.5 In the latter study, an adenine (A) to cytosine (C) conversion 444 bp upstream in 5′-flanking region of the LTC4S gene (Figure) was overrepresented in AIA.5 Subsequent studies, which either confirmed6 or did not replicate7–9 the genotype effect, in addition suggested that the cysteinyl-LTs, exert their actions by means of at least 2 subclasses of CysLT receptors (Figure) expressed in airway and vessels, as well as on inflammatory cells. The CysLT1 receptor is the target for the clinically used antileukotrienes in asthma: montelukast, zafirlukast and pranlukast (Figure). The gene for LTC4S is mapped to the chromosome region 5q35, which is close to the cluster of cytokine genes associated with Th2 responses and asthma.2

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In contrast to the overrepresented −444 C in AIA,3 the study by Freiberg et al associates the same polymorphism with a decreased risk for ischemic cerebrovascular events.4 Because LTC4 synthesis has been reported to be enhanced in calcium ionophore-stimulated eosinophils derived from carriers of C at the −444 locus,6 the main question raised by those results is hence whether cysteinyl-LTs are protective or deleterious in cerebrovascular disease. Although genotyping without evaluation of the functional consequences cannot give the verdict to cysteinyl-LTs as being angels or demons, some interesting hypotheses can be generated by integrating findings in cardiovascular cohorts with those previously reported in the context of asthma.

Whereas asthmatics with the genotype described as protective for cerebrovascular events4 display an increased cysteinyl-LT biosynthesis,6 the genotype effect in stroke patients remains unknown given the lack of LT measurements in the studies evaluating genetic LTC4S variations in the context of cardiovascular disease.4,10 Furthermore, the rationale for the initial studies of AIA was based on the selective upregulation of LTC4S in bronchial biopsies from these patients.11 In contrast, human carotid atherosclerotic lesions have been reported not to express increased levels of LTC4S compared with healthy vessels.12 Nevertheless, although LTC4S may not be as profoundly upregulated in the vascular wall as has been reported in bronchial mucosa, the atherosclerotic lesion is indeed a site of local cysteinyl-LT production.13 Because the cellular composition of the eosinophilic bronchial inflammation in asthmatics may differ from the more macrophage-dominated atherosclerotic lesion, a cell-specific transcriptional regulation of the LTC4S gene cannot be excluded as explanation for the diverging promoter polymorphism-induced risk in asthma and cerebrovascular disease.

Furthermore, the finding that the −444 A to C conversion provides significant protection against stroke4 is also in contrast to another recent study reporting a significant correlation of the same SNP with increased coronary calcium and carotid intima media thickness (IMT) in women.10 These apparent contradictory results raise the possibility of a time-dependent role of cysteinyl-LTs in cardiovascular disease. Whereas progression of atherosclerosis (measured as coronary calcium and IMT10) potentially could be promoted by cysteinyl-LTs, plaque rupture and stroke4 may be prevented if cysteinyl-LT production increases. One possible mechanism in this time-dependency could be related to cysteinyl-LT-induced effects on vascular smooth muscle cells (SMCs). Cysteinyl-LTs induce SMC proliferation and intimal hyperplasia1 and may through this mechanism of action act as demons in the atherosclerosis process. However, could cysteinyl-LTs subsequently act as angels by stimulating SMCs to stabilize the plaque?

The latter question remains unanswered, because the exact role and time-course of the cysteinyl-LT–induced effects on SMCs and on other cells within the atherosclerotic lesion today are largely unknown. In contrast, the other arm of the...
LT cascade, namely the chemotactic LTB₄ (Figure), has been more extensively studied in this context. Selective inhibition of LTB₄ signaling through BLT receptors has shown beneficial effects in different animal models of atherosclerosis. Another tempting hypothesis is that an upregulation of LTC₄S potentially could shunt LTA₄ metabolism toward LTC₄ and hence diminish LTB₄ production (Figure). Again, in the absence of explorations of the functional genotype effect, this latter suggestion remains rather speculative for the moment.

Finally, it should be pointed out that LTC₄S is only 1 of 3 enzymes which can conjugate LTA₄ with glutathione to cysteinyl-LTs. Also other enzymes within the mGST family can participate in cysteinyl-LT biosynthesis, but have not yet been explored in the context of atherosclerosis.

A potential stroke-protective effect of proinflammatory mediators is definitively an exciting thought. However, although promoter polymorphisms only can provide a suggestion of such a link, further mechanistic studies are needed before judging the cysteinyl-LTs as either angels or demons in cerebrovascular disease.

Disclosures

None.

References

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