ABCA1 and Inflammation
From Animal Models to Humans

Xin Bi, Cecilia Vitali, Marina Cuchel

A TP-binding cassette transporter subfamily A member 1 (ABCA1) is a plasma membrane protein well known for its role in regulating cellular cholesterol efflux and high-density lipoprotein (HDL) formation.1 Carriers of loss-of-function mutations in ABCA1 are characterized by reduced HDL cholesterol levels, which are nearly absent in the rare homozygous state (Tangier disease), and accumulation of cholesterol in several tissues, especially those rich in macrophages and reticuloendothelial cells.2 Although patients with Tangier disease are characterized by decreased cholesterol efflux from fibroblasts and increased carotid wall thickness when compared with control subjects,3,4 specific ABCA1 deficiency has highlighted its role as a master regulator of cellular cholesterol homeostasis that goes well beyond the formation of HDL particles and macrophage reverse cholesterol transport. These studies have, for example, demonstrated ABCA1 expression in the neurons and glia, where it may affect amyloid burden5 and neuroinflammation6; in the retina, where it may be responsible for the accumulation of membrane lipids observed with aging and related pathologies;7 in the pancreatic β cells, where it may play a crucial role in insulin secretion;8 and in myeloid cells, where it contributes to proliferation and mobilization of progenitor cells, and activation of neutrophils and monocytes.9 The ability of ABCA1 to mobilize cellular cholesterol and efflux it to acceptor particles, as well as its direct involvement in signaling pathways3 may contribute to these effects. Translating findings from in vitro and inbred animal models into humans is not straightforward, as demonstrated by conflicting results in the role of ABCA1 in insulin secretion,10,11 Alzheimer disease12 and even in cardiovascular risk.13,14

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Cholesterol efflux from macrophages has been shown to be predictive of cardiovascular events and their incidence.5,6 ABCA1 is generally considered atheroprotective for its ability to mediate this first step of the reverse cholesterol transport pathway.7

In recent years, the use of animal models with tissue-specific ABCA1 deficiency has highlighted its role as a master regulator of cellular cholesterol homeostasis that goes well beyond the formation of HDL particles and macrophage reverse cholesterol transport. These studies have, for example, demonstrated ABCA1 expression in the neurons and glia, where it may affect amyloid burden and neuroinflammation; in the retina, where it may be responsible for the accumulation of membrane lipids observed with aging and related pathologies; in the pancreatic β cells, where it may play a crucial role in insulin secretion; and in myeloid cells, where it contributes to proliferation and mobilization of progenitor cells, and activation of neutrophils and monocytes. The ability of ABCA1 to mobilize cellular cholesterol and efflux it to acceptor particles, as well as its direct involvement in signaling pathways may contribute to these effects. Translating findings from in vitro and inbred animal models into humans is not straightforward, as demonstrated by conflicting results in the role of ABCA1 in insulin secretion, Alzheimer disease and even in cardiovascular risk. However, the relevance of these animal and in vitro data in humans is not clear, especially when taking into consideration that the more pronounced proinflammatory effect resulting from cellular cholesterol accumulation is seen in macrophage double knockout animal models lacking both ABCA1 and ABCG1, an engineered condition that is highly unlikely to be seen in humans.

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Bochem et al present evidence that partial or total ABCA1 deficiency is associated with a proinflammatory status in humans (Figure). To test their hypothesis, the authors enrolled subjects carrying loss-of-function mutations in ABCA1 to undergo a set of tests that included carotid MRI, 18F-fluorodeoxyglucose positron emission tomography/computed tomography, plasma cytokine level measurements, inflammatory gene expression in circulating monocytes and in human monocyte-derived THP-1 cells incubated with polyethylene glycol-precipitated and lipoprotein-deficient plasma obtained from study subjects. Results obtained in carriers of ABCA1 mutations were compared with age- and sex-matched controls.

Significant increase in vessel wall inflammation (assessed by positron emission tomography/computed tomography) and systemic inflammation (assessed by plasma cytokine levels and inflammatory gene expression in circulating monocytes) were observed in carriers versus controls. Interestingly, tumor necrosis factor-α was the only cytokine that showed a gene dose increase in plasma levels and increased mRNA expression in circulating monocytes isolated from carriers, suggesting that other factors in addition to ABCA1 deficiency may have contributed to the results. In particular, because HDL has been shown to have anti-inflammatory properties, it cannot be excluded that the low levels of HDL present in the carriers contributed to the observed proinflammatory
status. The increase in cytokine expression in THP-1 cells incubated with polyethylene glycol-precipitated plasma support this possibility. As a note of interest, vessel wall inflammation and plasma levels of tumor necrosis factor-α were not different from control in carriers of functional mutations in ABCA1 treated with statins. This intriguing finding is evidence of a beneficial anti-inflammatory effect of statins in these patients independent of their low-density lipoprotein-cholesterol levels.

Although these results need to be confirmed and more studies will be necessary to better investigate the contribution of ABCA1 deficiency versus that of HDL levels, this study is a first important step in translating a significant and convincing body of work in animals into humans. It also highlights that deep-phenotype characterization of subjects affected by Mendelian
disorders provides an excellent strategy for direct interrogation of the role of genes of interest in human complex polygenic disorders, such as atherosclerotic cardiovascular disease.

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Disclosures

None.

References


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