ABCA1 and Inflammation
From Animal Models to Humans

Xin Bi, Cecilia Vitali, Marina Cuchel

Macrophage-specific ABCA1 deficiency is associated with increased proinflammatory gene expression and cytokine release both in vivo in animal models and in vitro (Figure). The enhanced macrophage proinflammatory response is linked to the myeloid differentiation primary response 88-dependent mobilization of Toll-like receptors, including Toll-like receptor 4, to lipid rafts. This phenomenon is a consequence of free cholesterol accumulation in the lipid rafts in the context of ABCA1 deficiency. Fibroblasts from a patient with Tangier disease displayed similar features. It has also been shown that an apoipoprotein A-I/ABCA1 interaction activates the Janus kinase 2/signal transducer and activator of transcription 3 pathway, which suppresses inflammatory responses in macrophages independent of the lipid transport function of ABCA1. Thus, ABCA1 within the macrophage may confer atheroprotection, not only through its ability to promote reverse cholesterol transport but also through its ability to modulate the inflammatory response.

However, the relevance of these animal and in vitro data in humans is not clear, especially when taking in 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 monocye-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 supports 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

Figure. Potential mechanisms underlying increased inflammatory status in ATP-binding cassette transporter subfamily A member 1 (ABCA1)-deficient subjects. A, ABCA1 plays a major role in nascent high-density lipoprotein (HDL) formation and cellular cholesterol homeostasis. Excess free cholesterol (FC) and phospholipid in peripheral tissues, including macrophages in the arterial wall, can be transported out of cells through active lipid efflux via transporters such as ABCA1 into HDL. Through this process ABCA1 can modulate the amount of FC present in the plasma membrane. ABCA1-mediated reduction in membrane FC content leads to decreased membrane lipid raft content. This dampens inflammatory signaling by reducing Toll-like receptors (TLRs) in lipid rafts on macrophages in a myeloid differentiation primary response 88 (MyD88)-dependent manner. ApoA-I and ABCA1 interaction activates Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3), which suppresses proinflammatory genes such as tumor necrosis factor-α (TNF-α).

B, ABCA1 deficiency leads to a marked decrease in HDL formation and impaired cholesterol efflux from the macrophages. Accumulation of FC in plasma membrane mobilizes TLRs (eg, TLR4) to lipid rafts. This, in turn, enhances MyD88-dependent TLR inflammatory responses. ABCA1 deficiency also impairs the JAK2/STAT3 anti-inflammatory pathway. Both ABCA1 deficiency and reduced circulating HDL levels may contribute to the increased plasma cytokine levels. The proinflammatory status observed in subjects carrying ABCA1 mutations may be reduced by statin treatment. Dashed lines, negatively affecting; solid line, positively affecting. IL indicates interleukin; NF-κB, nuclear factor-κB; and SR-BI, scavenger receptor class B member 1.
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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None.

**References**

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