Austin Journal of Pharmacology and Therapeutics

Austin Publishing Group

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Editorial

ABCC6 Out From the Cold: Identification of the ABCC6 Substrate as a Therapy for Pseudoxanthoma Elasticum and Cardiovascular Disease

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Received: July 22, 2014; **Accepted**: July 27, 2014; **Published**: Aug 04, 2014

ABCC6 is a member of the ATP-Binding Cassette family of transporters. This diverse family of 50 proteins are involved in efflux transport of a wide variety of substrates important in several diseases including cardiovascular disease [1] and Pseudoxanthoma Elasticum [2]. This rare, progressive disease leads to a specific clinical profile, including calcified dermatological lesions, defects in Bruch's membrane of the retina leading to bilateral blindness, and broad effects in several organs associated with aberrant calcification [3]. The substrate for ABCC6 has yet to be defined, and this remains an important research target that may affect clinical outcomes.

Emerging studies suggest that ABCC6 plays an important role in cardiovascular disease, which warrants further study. SNPs within the ABCC6 gene have been associated with cardiovascular disease in human populations [4-6], and several clinical reports have defined cardiovascular complications in PXE patients with accompanying ABCC6 mutations [7-9]. These studies highlight a role for ABCC6 gene heterozygosity in cardiovascular disease. However, incomplete penetrance of the cardiovascular disease phenotype in the setting of PXE where patients are homozygous null is paradoxical.

ABCC6 over expression and deficient mouse models have been informative in answering questions relating Abcc6 and cardiovascular disease. Using integrative genomics and transgenic overexpression in the mouse model system, Abcc6 was identified as a major causal gene in cardiac calcification using the inbred C3H/HeJ strain [10]. The excessive cardiac calcification phenotype is also noted in the engineered Abcc6 knockout model [11]. Importantly, recent reports have shown increases in infarct size in C3H and Abcc6 knockout mice using cardiac ischemia reperfusion and myocardial infarction models [11,12]. Conversely, a protective effect due to transgenic Abcc6 overexpression in the cardiac ischemia reperfusion model has also been demonstrated [11,12]. Collectively, these data suggest that a defect in Abcc6 activity may contribute to worsening outcomes in the setting of cardiovascular disease and acute myocardial infarction.

A recent study comparing the polar bear and brown bear genomes identified ABCC6 and APOB as two of the top 20 genes undergoing positive selection [13]. APOB plays an important role in removing artery clogging LDL from the bloodstream, and polar bears have a diet comparably that is high in fat. An intriguing hypothesis put forth by the authors was that changes in the ABCC6 gene have accompanied polar bear adaption to a high fat diet, owing to a mechanistic contribution of this gene affecting cardiovascular function.

ABCC6 has highest expression in the liver and kidneys, and its substrate likely exerts effects through the circulation. The identity of the circulating ABCC6 substrate would inform a strategy to replace this factor in the setting of human disease. Direct applications include treatments for the rare disease PXE and reversal of pathology. Additionally, in the setting of cardiovascular disease the ABCC6 substrate may have a wider impact on clinical therapy. The established mouse models provide avenues to test the efficacy of this factor in affecting outcomes follow cardiac ischemia. These models may also be used to address whether pharmacological supplementation affects vascular calcification and development of atherosclerosis using established models. Future studies in the area should highlight more precisely the roles for ABCC6 in affecting human cardiovascular disease population wide. Established mouse and in vitro model systems are available to test therapeutic avenues for the substrate for ABCC6. The identity of the substrate for ABCC6 is thus of considerable interest with significant clinical potential.

Source Funding: This work was supported by NIH-NHLBI Grant #HL094709.

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Citation: Prescott ET and Mungrue IN. ABCC6 Out From the Cold: Identification of the ABCC6 Substrate as a Therapy for Pseudoxanthoma Elasticum and Cardiovascular Disease. Austin J Pharmacol Ther. 2014; 2 (5).2

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Austin J Pharmacol Ther - Volume 2 Issue 5 - 2014
ISSN: 2373-6208 | www.austinpublishinggroup.com

Citation: Prescott ET and Mungrue IN. ABCC6 Out From the Cold: Identification of the ABCC6 Substrate as a Therapy for Pseudoxanthoma Elasticum and Cardiovascular Disease. Austin J Pharmacol Ther. 2014; 2 (5).2