EBioMedicine 2 (2015) 1864–1865

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Genetic Susceptibility to Oxidative Stress and Cardiovascular Disease

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ARTICLE INFO

Article history:
Received 25 November 2015
Accepted 25 November 2015
Available online 2 December 2015

Cardiovascular disease continues to be the leading cause of death in patients with Type-2 Diabetes Mellitus (T2D). Aggressive use of HMG-CoA Reductase Inhibitors (statins) and blood pressure lowering agents are showing signs of success as rates of coronary heart disease are on the decline (Ali et al., 2013); however, a substantial amount of residual risk remains suggesting that additional prevention strategies are needed particularly in light of recent increases in the prevalence of T2D (Gregg et al., 2007).

Treatments that block the damaging effects of oxidants have long been considered as potential strategies to reduce the risk of cardiovascular disease. Because redox signaling in the heart and other tissues can have both physiological and pathological effects (Burgoyne et al., 2012) any benefit from anti-oxidant therapies may be limited. Indeed, while Vitamin E showed benefit in a mouse atherosclerosis model (Pratico et al., 1998) and observational studies showed an inverse association of Vitamin E intake and cardiovascular disease (Jha et al., 1995), randomized double blind placebo controlled trials do not support a benefit from Vitamin E, and even suggested harm (Lonn et al., 2005). The discordant results of anti-oxidant clinical trials compared with observational and experimental studies raise many considerations including whether clinical trials testing anti-oxidant compounds should target enrollment of subjects that have increased oxidant stress (Robinson et al., 2006).

In this issue of *EBioMedicine*, Kobylecki et al. contribute to our understanding of the role of the natural anti-oxidant system plays in cardiovascular disease through their analysis of the Copenhagen General Population Study and the Copenhagen City Heart Study (Kobylecki et al., 2015). The authors studied a single nucleotide polymorphism in the extracellular superoxide dismutase-3 gene (SOD3) that results in the exchange of an amino acid causing the SOD3 peptide to not be retained in the blood vessel wall. Diabetic individuals heterozygous for this SOD3 variant were found to have an increased risk of cardiovascular disease while strikingly there was no signal in subjects without diabetes. These findings, supported by independent studies (Mohammedi et al., 2015), suggest that some individuals have a genetically-driven impairment of anti-oxidant defenses that predispose them to cardiovascular disease in states of oxidant stress such as diabetes. What is currently unknown is whether restoring anti-oxidant defenses in people that carry the SOD3 polymorphism abrogates the additional risk of cardiovascular disease.

Two points should be emphasized. First, despite the negative findings of previous randomized clinical trials this study and others like it should motivate the continued development and testing of novel anti-oxidant compounds to prevent cardiovascular disease, particularly in genetically susceptible individuals that have T2D. Second, genetic studies continue to identify meaningful insight into disease pathogenesis when results from animal and clinical studies conflict.

We are on the verge of realizing the benefits of Precision Medicine in cancer therapy through the use of genetic information to guide treatment selection (Collins and Varmus, 2015). While the current use of genetics to guide the prevention of cardiovascular disease is in its infancy, clinical trials that focus on genetically at risk individuals may have the strongest ability to demonstrate a proof-of-principle for the potential benefits of novel treatments.

Disclosure

The author declared no conflicts of interest.

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DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2015.11.026.
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http://dx.doi.org/10.1016/j.ebiom.2015.11.042
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