CORONARY ARTERY DISEASE IL-6 SIGNALING LINKED WITH CHD

A genetic variant in the IL-6 receptor (IL6R) is associated with a reduced risk of coronary heart disease (CHD). IL6R blockade is, therefore, a rational and novel therapeutic approach to prevent CHD. “Whilst it has long been suspected that inflammation plays a role in the development of CHD, previous well-studied inflammation biomarkers (such as C-reactive protein [CRP] and fibrinogen) have been suggested not to play a causal role,” explains Dr Adam Butterworth from the IL6R Genetic Consortium.

Membrane-bound IL6R is activated by circulating IL-6, which initiates proinflammatory hepatic production of CRP and fibrinogen. Dr Butterworth and colleagues studied the Asp358Ala variant in *IL6R*, which is thought to reduce levels of membrane-bound IL6R, in a meta-analysis of 125,222 individuals from 82 studies. The minor allele frequency was 39%, and was not associated with differences in conventional CHD risk factors (lipid concentrations, blood pressure, adiposity, or dysglycemia), but was associated with reduced levels of CRP and fibrinogen. Furthermore, the risk of CHD was reduced by 3.4% (95% CI 1.8–5.0) for every copy of 358Ala inherited.

In another meta-analysis of up to 133,449 individuals from 40 studies, the Asp358Ala variant was similarly associated with reduced levels of CRP, fibrinogen, and CHD risk (OR 0.95, 95% CI 0.93–0.97). Dr Daniel Swerdlow and colleagues from the IL6R MR Consortium found that the changes in inflammatory markers were consistent with the effects of the IL6R inhibitor tocilizumab, which is used to treat rheumatoid arthritis. This “novel etiological pathway ... may present opportunities for new [CHD] preventive strategies that target inflammatory processes,” says Dr Swerdlow. However, “tocilizumab is administered by monthly intravenous infusions and is, therefore, unsuitable for use in population-level prevention.” Furthermore, “the drug seems to cause an adverse lipid profile,” cautions Dr Butterworth. Both consortia will continue to study the complex IL-6 signaling pathway as a target for CHD prevention.

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Original articles IL6R Genetics Consortium and Emerging Risk Factors Collaboration. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. *Lancet* doi:10.1016/S0140-6736(11)61931-4 | The Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. *Lancet* doi:10.1016/S0140-6736(12)60110-X