BIOBUSINESS BRIEFS

TRIAL WATCH

Genetic association studies link interleukin-6 receptor to coronary heart disease

Two studies published in *The Lancet* indicate that the interleukin-6 receptor (IL-6R) has a causal role in the development of coronary heart disease (*Lancet* **379**, 1214–1224; 2012; *Lancet* **379**, 1205–1213; 2012).

IL-6 is a pro-inflammatory cytokine that has a key role in several disorders, such as rheumatoid arthritis and Crohn's disease. Previous observational studies have suggested a link between IL-6 and heart disease but such studies were unable to establish whether this relationship is causal.

Both of the current studies investigated a single nucleotide polymorphism (SNP) in the *IL6R* gene (rs2228145; Asp358Ala), which is thought to lead to impairment of IL-6R-mediated signalling. The authors collected data from well-established clinical studies to compare the frequency of the genetic variant in patients with coronary heart disease and in controls. They found that the SNP was associated with an increased plasma IL-6 concentration and a reduced risk of coronary heart disease.

"I believe that these two genetic studies provide the first substantive findings in favour of a causal role in coronary heart disease for a specific inflammatory pathway," says Daniel Swerdlow, Department of Epidemiology and Public Health, University College London, UK, who was lead author of one of the studies. "Importantly, because a specific inhibitor of IL-6 signalling (tocilizumab) is already in routine use for the treatment of rheumatoid arthritis, the pathway is known to be safely and tolerably druggable in humans," he adds.

The study led by Swerdlow analysed data from over 133,000 individuals, and showed that the Asp358Ala SNP was associated with an increased log IL-6 concentration of 9.45% per allele, and a 5% lower odds ratio of coronary heart disease per allele. This study also analysed data from patients with rheumatoid arthritis who had been treated with tocilizumab, and showed that the drug increased levels of IL-6 and soluble IL-6R. The second study, from the University of Cambridge, UK, studied over 187,000 individuals and showed that for every copy of 358Ala inherited, the mean concentration of the soluble IL-6R increased by 34.3%, IL-6 concentration increased by 14.6% and the risk of coronary heart disease was reduced by 3.4%.

The link between increased concentrations of IL-6 (and soluble IL-6R) and heart disease might appear to be contradictory. But the authors note that reduced IL-6R signalling — caused by the genetic variant or by tocilizumab — could remove feedback inhibition of IL-6 release or modulate the clearance of IL-6 via the IL-6R, but is unlikely to influence IL-6 production.

Although the studies suggest that blockade of IL-6-mediated signalling could prevent coronary heart disease, tocilizumab and similar drugs in development are unlikely to be suitable for large-scale prevention because they need to be administered by injection.

The methods used in these studies, namely the study of genetic variants to link the effects of pharmacologically modulating a signalling pathway in a study population (sometimes referred to as Mendelian randomization analysis), could also be used to investigate other drugs and targets. For example, Swerdlow's group and collaborators have used this methodology to investigate the adverse blood pressure-raising effect of the cholesteryl ester transfer protein inhibitor torcetrapib, and the potential of lipoprotein-associated phospholipase A2 as a drug target for the prevention of coronary heart disease. "Mendelian randomization appears to hold great promise for the identification of novel drug targets and their prioritization for future development, and also for the repurposing of existing targets for new clinical indications," he concludes.

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