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Genetic studies lay the foundations for anti-inflammatory drugs to prevent heart disease

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Two large international meta-analyses published Online First in *The Lancet* provide compelling new evidence that interleukin-6 receptor (IL6R), a protein involved in inflammatory signaling, has a causal role in the development of coronary heart disease (CHD). The findings suggest that drugs that target this specific inflammatory mechanism (ie, IL6R-mediated signaling) might also be effective in combating CHD. One such drug, tocilizumab, is already commonly used to treat rheumatoid arthritis*.

CHD is the leading cause of death worldwide. It is caused by atherosclerosis, a build-up of fatty material in the walls of arteries. There has been considerable interest in the role of inflammation in atherosclerosis, but until now, a direct causal link with a specific inflammatory biomarker has not been shown.

Previous studies have reported associations between various blood measures of inflammation and the risk of heart attacks, but human genetic studies have suggested that these simply reflect correlations rather than cause-and-effect relationships.

By contrast, in the first Article, the IL6R Genetics Consortium and Emerging Risk Factors Collaboration have reported that a genetic variation responsible for dampening inflammation reduces the risk of heart disease.

In particular, the researchers analysed genetic and biomarker

information from over 200 000 people in 82 studies to assess whether a functional genetic variant (Asp358Ala) in the IL6R gene, known to control IL6R signaling, might affect susceptibility to CHD. The 358Ala allele was associated with a clear anti-inflammatory effect, shown by reductions in levels of C-reactive protein and fibrinogen in the blood, as well as a 3.4% reduction in CHD risk for each copy of 358Ala inherited.

The authors say: "These results support the inflammation hypothesis in CHD and encourage exploration of modulation of IL6R pathways as a means to prevent CHD."

In a second Article, the IL6R Mendelian Randomisation Analysis Consortium analysed data from 40 studies involving almost 133 500 participants to examine whether using a drug to block the IL6 receptor from exerting its pro-inflammatory effects might reduce the risk of CHD in the general population.

Using Mendelian randomisation** they identified that a single-nucleotide polymorphism (SNP) gene variation in IL6R (rs7529229), which represents the Asp358Ala variant, had effects on several inflammatory markers and related pathways consistent with effects reported in trials blocking the IL6R in patients with rheumatoid arthritis using the drug tocilizumab.

A further meta-analysis predicted the same (rs7529229) variant was associated with a lower risk of CHD in a total of 25 458 CHD cases and 100 740 controls, corresponding to a 5% reduction in CHD risk for each copy inherited.

The authors conclude: "IL6R blockade could provide a novel therapeutic approach to prevention of CHD that warrants testing in suitably powered randomised trials."

In an accompanying Comment, Matthijs Boekholdt and Erik Stroes from the Academic Medical Center, Amsterdam, the Netherlands say: "Collectively, these large-scale and highly consistent results lend strong support to the concept that inhibition of inflammatory pathways is an attractive strategy to reduce cardiovascular risk."

More information: www.thelancet.com/journals/lan … (11)61931-4/abstract
www.thelancet.com/journals/lan … (12)60110-x/abstract

* Tocilizumab is known to reduce articular inflammation and promote disease remission in rheumatoid arthritis.
**Mendelian randomisation to validate drug targets uses variants in gene encoding of a drug target to profile the mechanism-based effects of pharmacological modification of that target, providing randomised evidence for the likely effectiveness of a new treatment without the potential risks of exposure to a novel drug or costs of a randomised trial.

Provided by Lancet